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Taga et al.

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(45) **Date of Patent: Oct. 29, 2013**

(54) **YS68 POLYPEPTIDE INVOLVED IN PRIMITIVE HEMATOPOIESIS**

(75) Inventors: **Tetsuya Taga**, Kumamoto (JP); **Naoki Kimura**, Ibaraki (JP)

(73) Assignee: **Chugai Seiyaku Kabushiki Kaisha**, Tokyo (JP)

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Related U.S. Application Data

(60) Division of application No. 11/643,069, filed on Dec. 20, 2006, now Pat. No. 7,794,973, which is a continuation of application No. 10/118,513, filed on Apr. 8, 2002, now abandoned, which is a continuation-in-part of application No. PCT/JP00/05756, filed on Aug. 25, 2000.

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(51) **Int. Cl.**
C07K 14/475 (2006.01)

(52) **U.S. Cl.**
USPC **530/350**; 530/838; 530/402

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Robert C Hayes
(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(57) **ABSTRACT**

A novel gene, dubbed "YS68", involved in primitive hematopoiesis was successfully isolated from cDNA derived from mouse yolk sacs. In addition, a human gene corresponding to this gene was successfully isolated. Expression characteristics of these genes suggested their involvement in primitive hematopoiesis. The proteins of this invention and genes encoding the proteins may be utilized as tools for drug development against diseases, such as hematological disorders.

13 Claims, 13 Drawing Sheets

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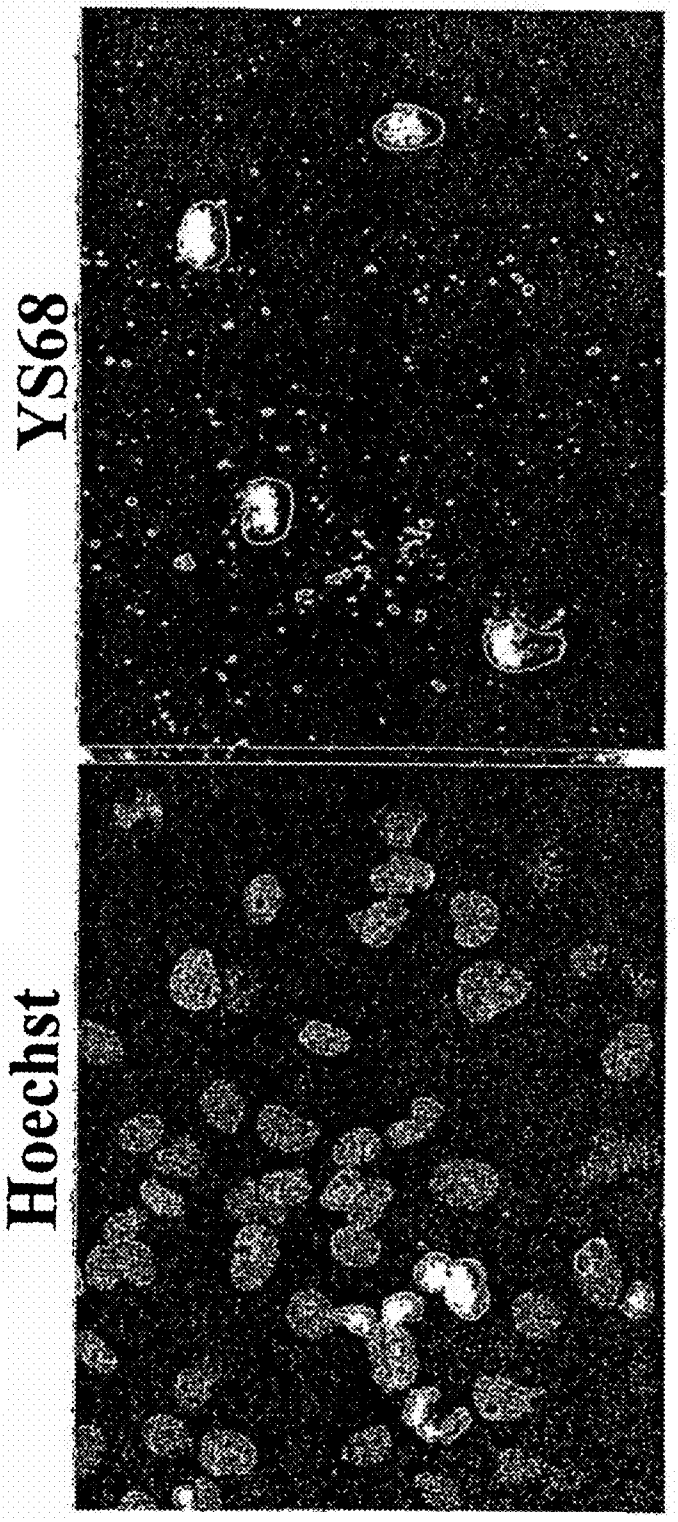


FIG. 1

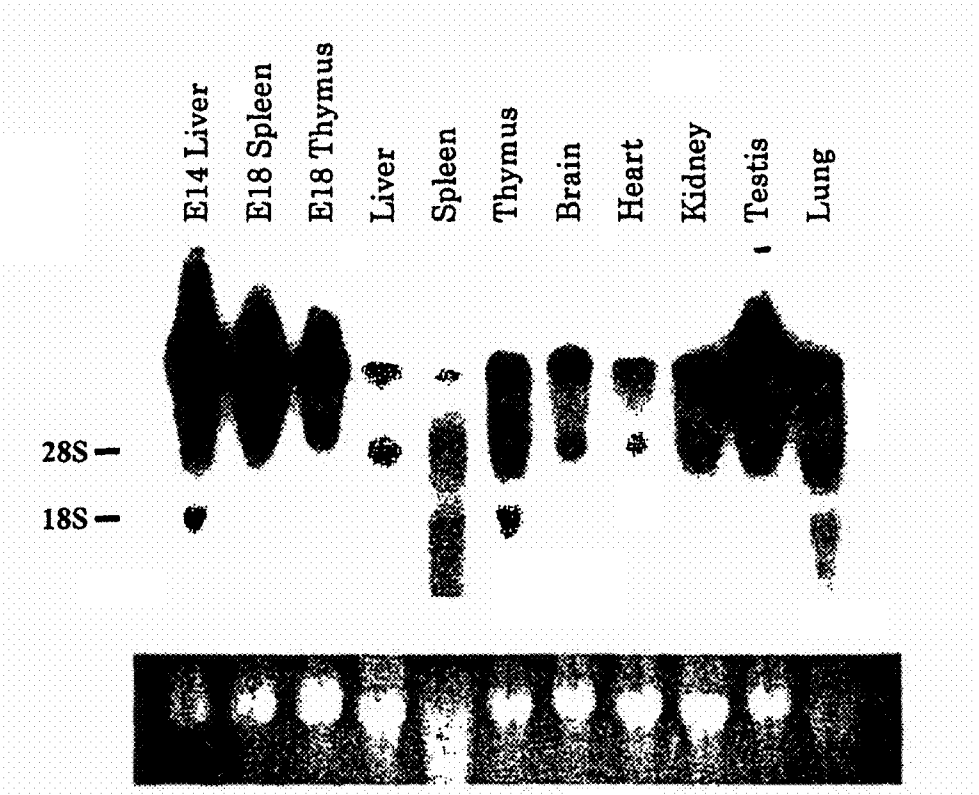

E14 Liver
E18 Spleen
E18 Thymus
Liver
Spleen
Thymus
Brain
Heart
Kidney
Testis
Lung
28S
18S

FIG. 2

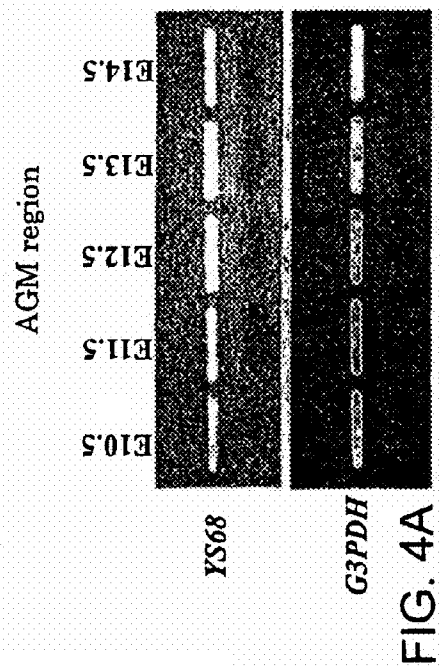


FIG. 4A

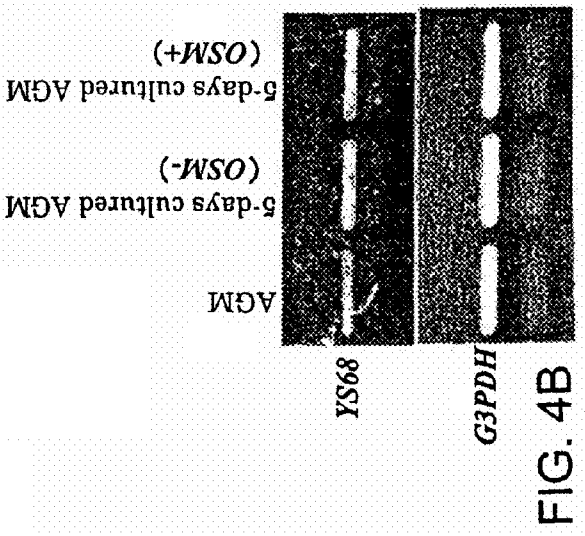


FIG. 4B

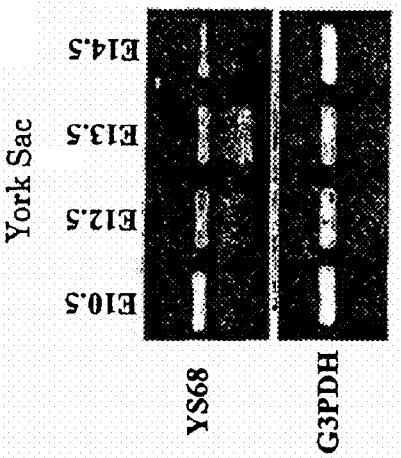


FIG. 3

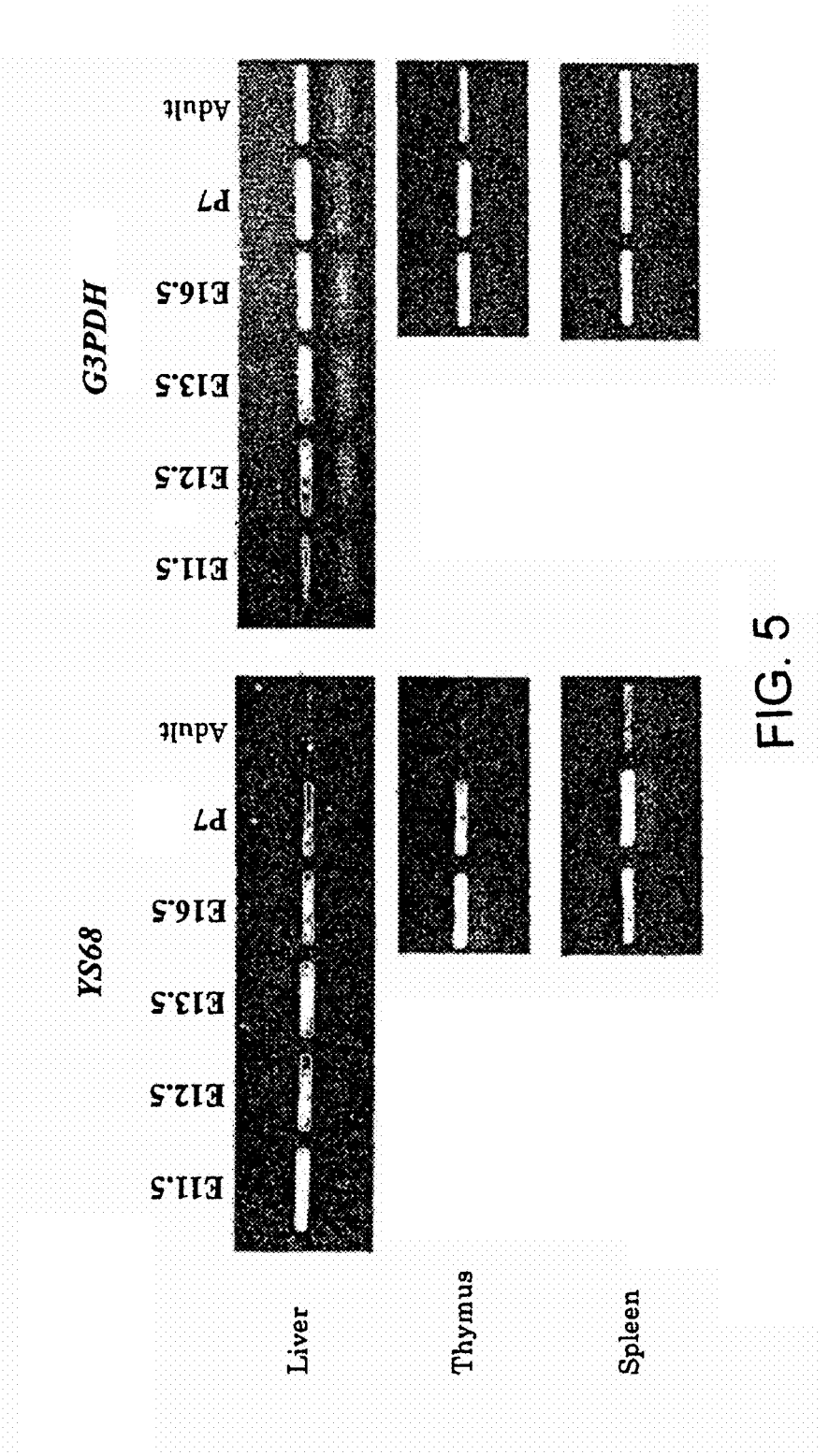


FIG. 5

FIG. 6A

FIG. 6B

FIG. 7A

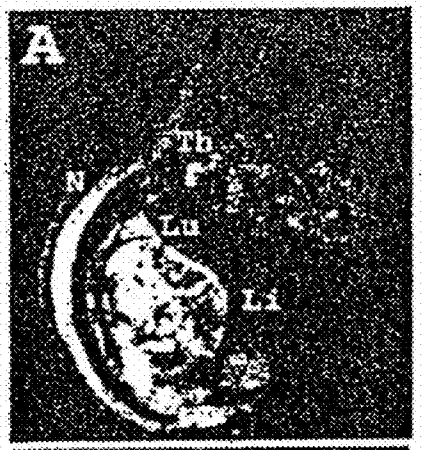
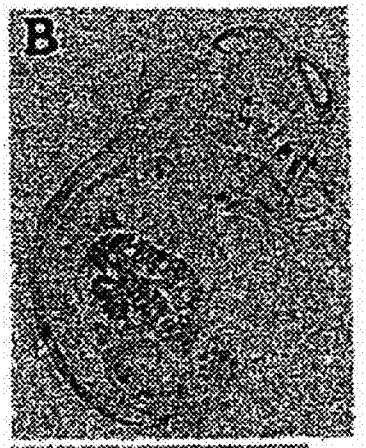


FIG. 7B



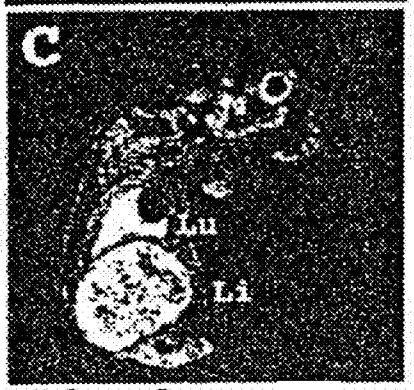


FIG. 7C

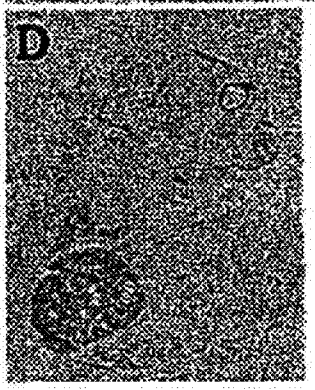


FIG. 7D

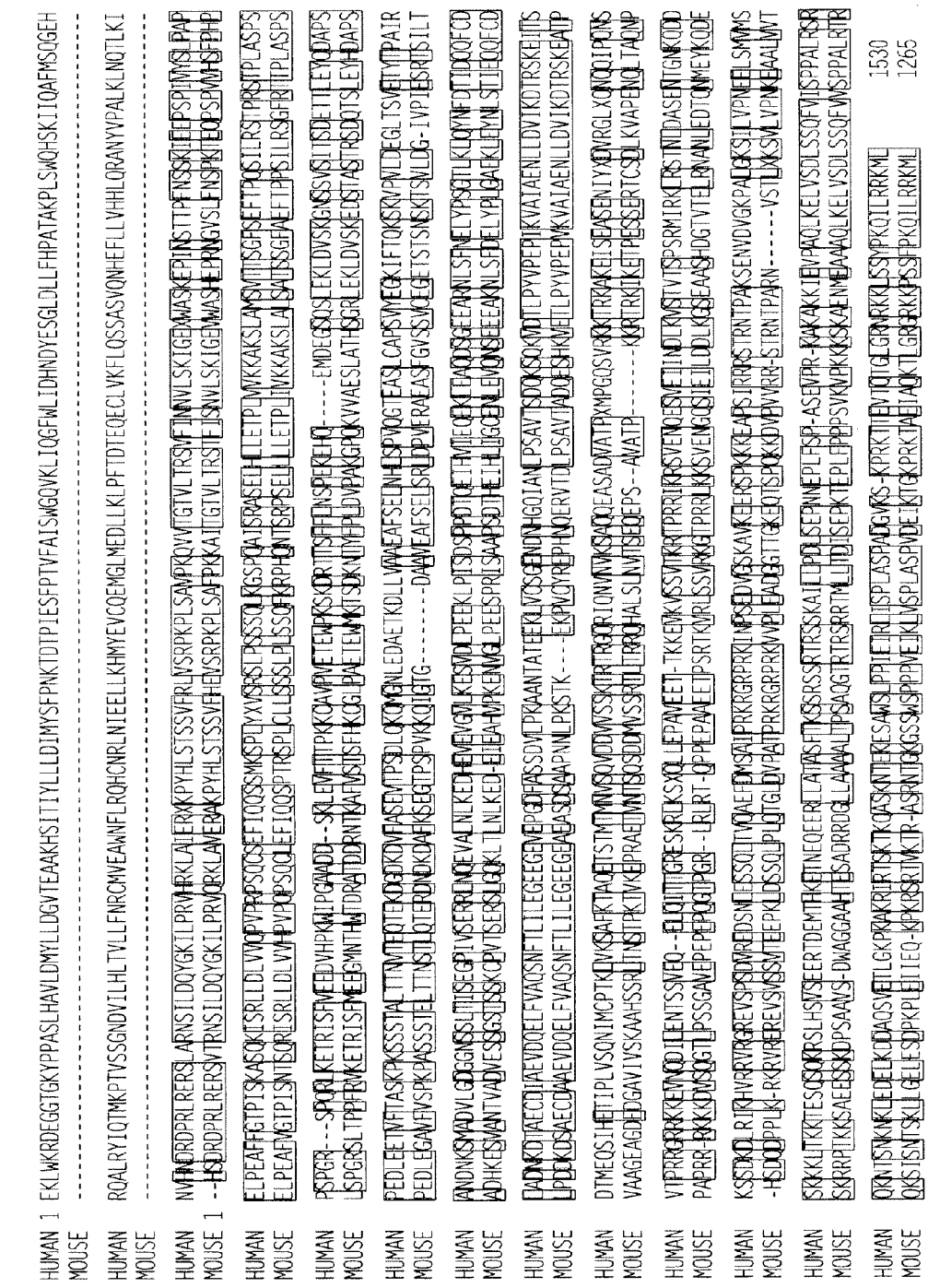


FIG. 8

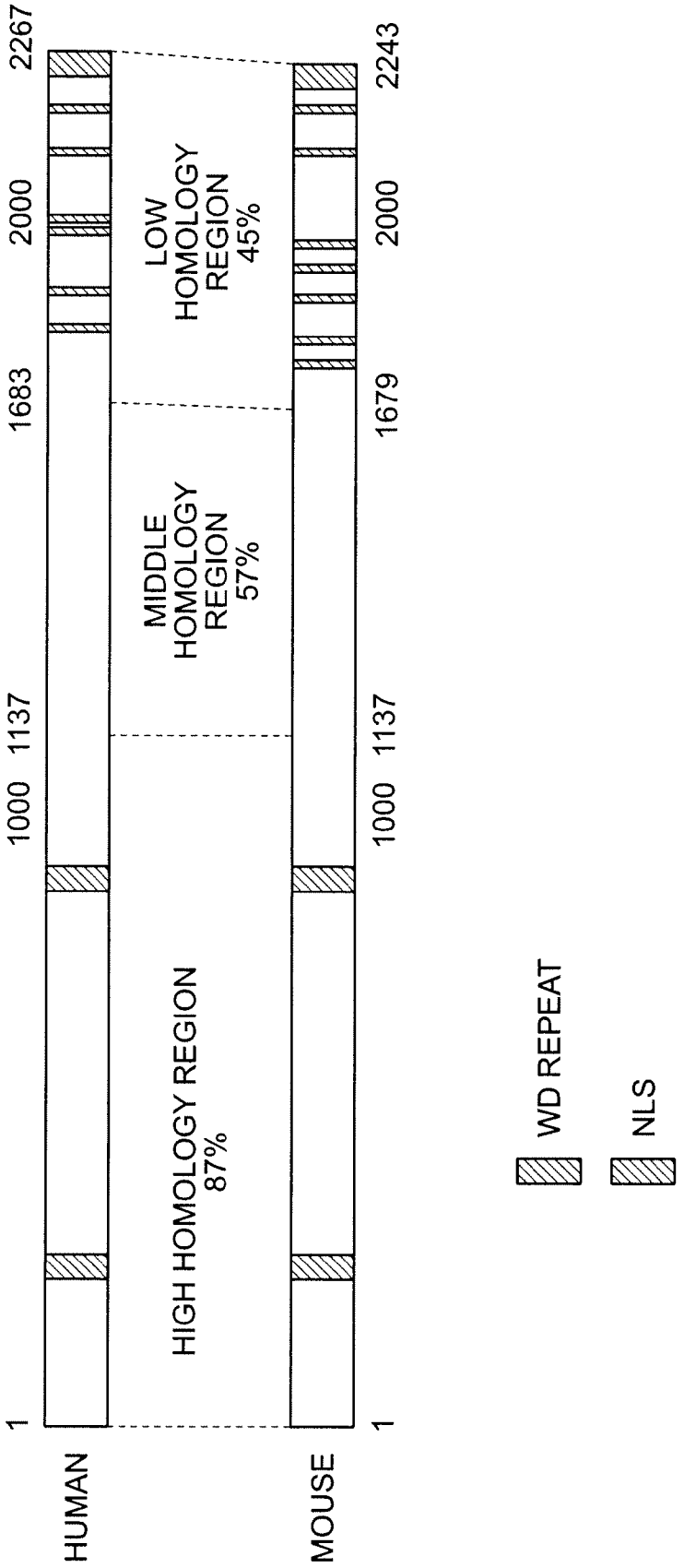

HUMAN
MOUSE
1
1000
1137
1683
2000
2267
1
1000
1137
1679
2000
2243
HIGH HOMOLOGY REGION
87%
MIDDLE
HOMOLOGY
REGION
57%
LOW
HOMOLOGY
REGION
45%
WD REPEAT
NLS

FIG. 9

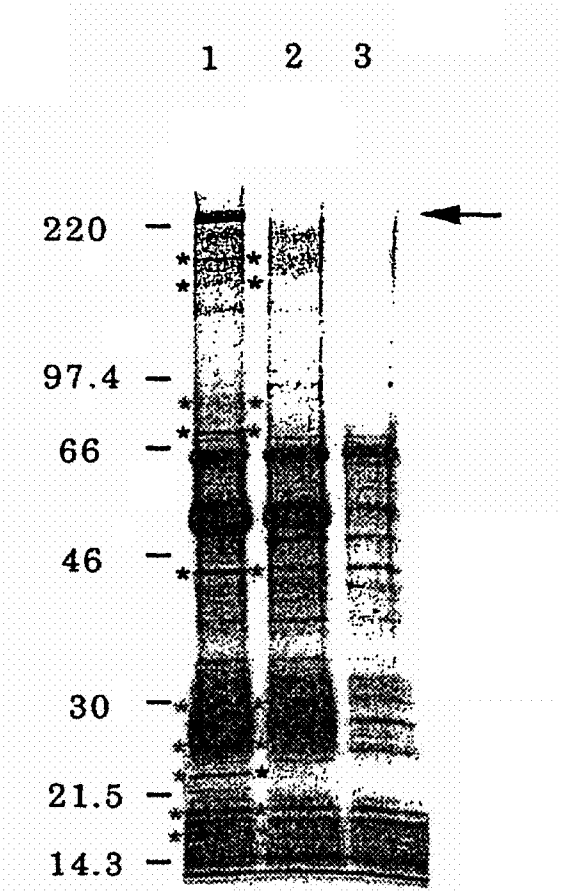


FIG. 10

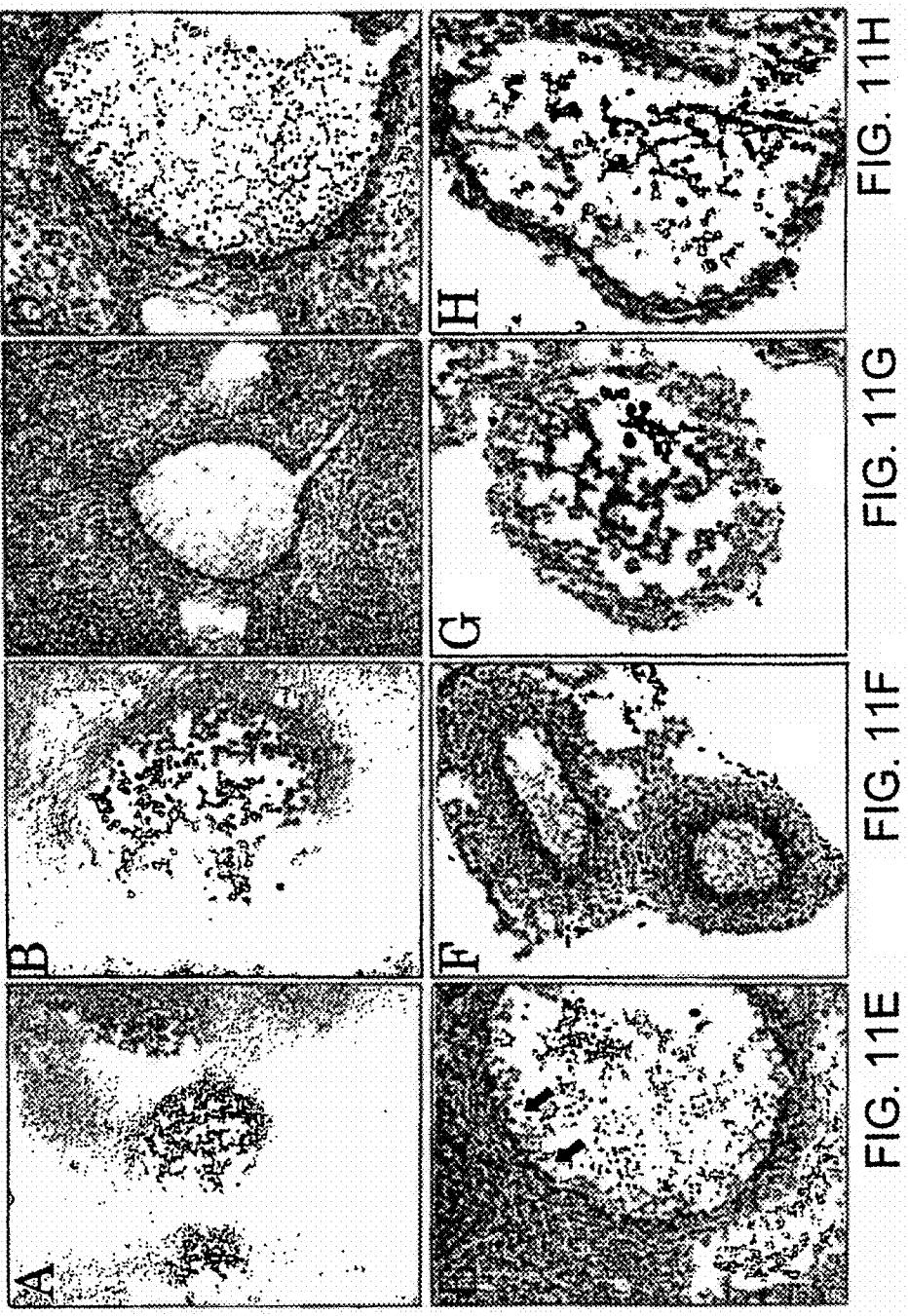


FIG. 11A FIG. 11B FIG. 11C FIG. 11D

FIG. 11E FIG. 11F FIG. 11G FIG. 11H

FIG. 12A

FIG. 12B

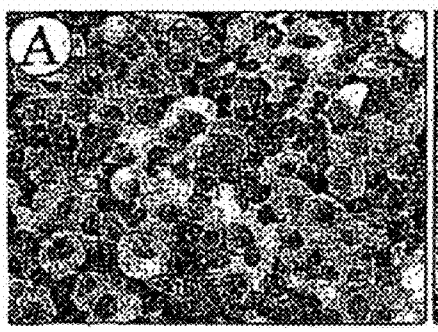


FIG. 13A

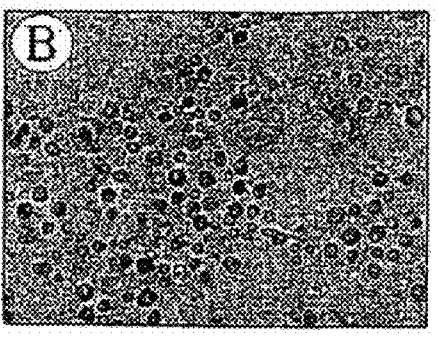


FIG. 13B

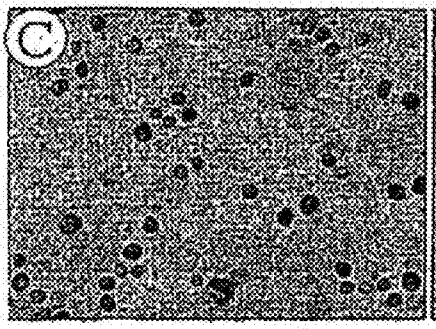


FIG. 13C

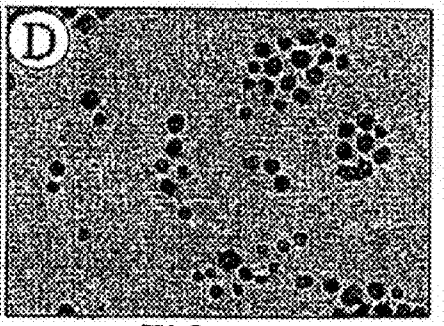


FIG. 13D

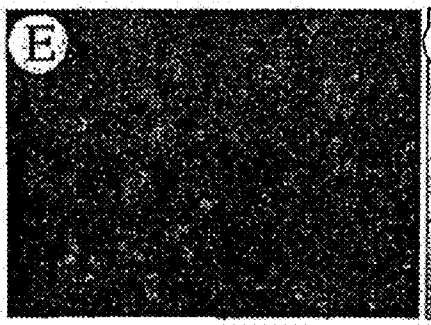


FIG. 13E

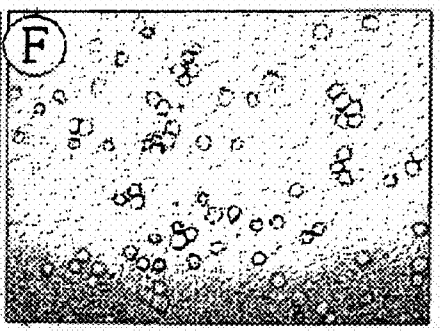


FIG. 13F

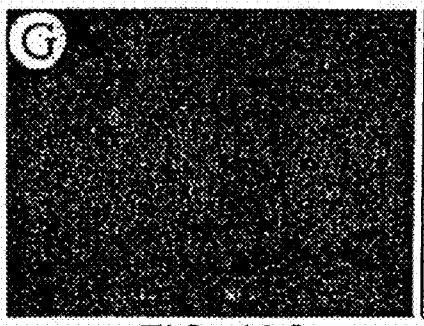


FIG. 13G

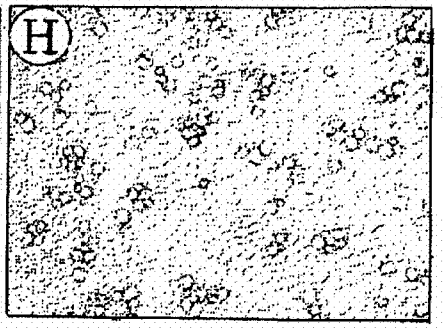


FIG. 13H

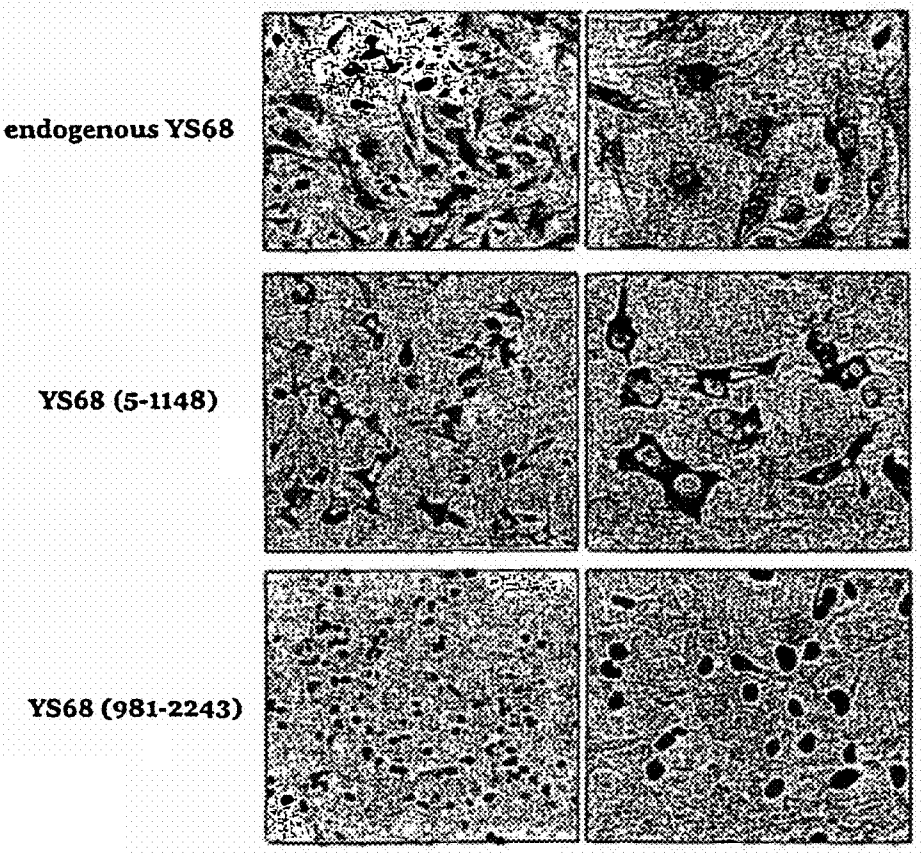


FIG. 14

YS68 POLYPEPTIDE INVOLVED IN PRIMITIVE HEMATOPOIESIS

This application is a divisional of U.S. patent application Ser. No. 11/643,069, filed Dec. 20, 2006, which is a continuation of U.S. patent application Ser. No. 10/118,513, filed Apr. 8, 2002 which is a continuation-in-part of International Patent Application PCT/JP00/05756, filed Aug. 25, 2000, which claims priority to Japanese patent application Ser. Nos. 11/288,738, filed Oct. 8, 1999; 11/288,739, filed Oct. 8, 1999; and 2000-123721, filed Apr. 19, 2000. The contents of these prior applications are incorporated by reference herein.

TECHNICAL FIELD

The present invention relates to novel proteins involved in primitive hematopoiesis and genes encoding the proteins. These molecules may be utilized, for example, in the field of drug development.

BACKGROUND

There are two kinds of hematopoiesis: one is the transient primitive hematopoiesis (embryonic hematopoiesis) that functions only during the embryonic stage, and the other is the definitive hematopoiesis (adult hematopoiesis) that contributes to lifelong hematopoiesis. Research by Medvinsky et al. (Medvinsky et al., Cell 86:897-906, 1996; Cumano et al., Cell 86:907-916) revealed that, in contrast to primitive hematopoiesis that develops within the yolk sac on around embryonic day 9, definitive hematopoiesis is initiated within the AGM (Aorta-Gonad-Mesonephros) region on around embryonic day 10. Furthermore, regarding the origin of hematocytes, various studies have suggested that definitive hematopoiesis originates from hemangioblasts, thought to be precursor cells common to hematopoietic cells and vascular endothelium cells.

While the mainly accepted view was that hemangioblasts, which are the origin of definitive hematopoiesis, exist in the AGM region, Yorder et al. argued against the existing theory and demonstrated that hemangioblasts, which may contribute to definitive hematopoiesis, also exist in the yolk sac (Yoder et al., Immunity 7:335-344, 1997). Therefore, it is now generally accepted that the surrounding environment is important for the differentiation of hemangioblasts to hematopoietic cells.

Thus, while the origin of hematopoietic cells and the site of development have been gradually elucidated by phenomenological research, the molecular mechanism of hematopoietic development remains unclear. The isolation of a novel molecule involved with primitive hematopoiesis is thought to be an important step for the development of unprecedented drugs associated with hematological disorders.

SUMMARY

The subject of the present invention is to provide novel proteins involved in primitive hematopoiesis and genes encoding the proteins, as well as production and use of the same.

Although the existence of hemangioblasts has been reported in the mouse AGM (Aorta-Gonad-Mesonephros) region on embryonic day 9 to day 12, Yorder and Nishikawa et al. have reported that hemangioblasts exist in embryonic day 9 yolk sacs, but no longer exist in embryonic day 13 yolk sacs (Yoder et al., Immunity 7:335-344, 1997; Nishikawa et al., Immunity 8:761-769, 1998). The present inventors conducted cloning of genes to identify molecules involved with primitive hematopoiesis by subtracting the cDNA derived from embryonic day 13 mouse yolk sac in which hemangioblasts are assumed to be absent, from the cDNA derived from embryonic day 9 mouse yolk sac in which hemangioblast is suggested to be present. Inventors succeeded in isolating a novel gene that was named "YS68". In addition, a primer was constructed based on the nucleotide sequence of the mouse gene, and, by performing 5'-RACE and 3'-RACE using human fetal liver Marathon-Ready cDNA as a template, the corresponding human gene was successfully isolated.

Determination and comparison of the full-length human (SEQ ID NO: 13) and mouse (SEQ ID NO: 11) cDNA sequences showed a very high sequence homology of 87% in the N-terminal region (human 1-1137 of SEQ ID NO: 13, mouse 1-1137 of SEQ ID NO: 11); whereas the homology in the central region (human 1138-1683 of SEQ ID NO: 13, mouse 1138-1679 of SEQ ID NO: 11) was 57%; and the homology in the C-terminal region (human 1684-2266 of SEQ ID NO: 13, mouse 1680-2243 of SEQ ID NO: 11) was very low at 45%. Many nuclear transport signals were found to exist in the low-homology C-terminal region. On the other hand, two WD repeats that are known to be necessary for interaction with proteins were found to exist in the high-homology N-terminal region.

To investigate the role of "YS68" in hematopoiesis, RT-PCR analysis of the expression pattern of "YS68" in mouse hematopoietic tissue was performed; the results revealed that the expression pattern of "YS68" correlated with the transport of hematopoietic tissues during the embryonic stage. In addition, "YS68" was expressed in CD34-positive undifferentiated hematocytes. Therefore, "YS68" is suggested to have an important function in primitive hematopoiesis.

The "YS68" protein of this invention is useful as a tool for elucidating the mechanism of primitive hematopoiesis, furthermore, its application to drug development for various diseases related to hematopoietic system is anticipated.

This invention relates to novel proteins involved in primitive hematopoiesis and genes encoding the proteins, as well as the production and use of the same. More specifically, this invention provides the following:

(1) a DNA selected from the group of:

(a) a DNA encoding a protein comprising the amino acid sequence of SEQ ID NO:12 or 14;

(b) a DNA comprising the coding region of the nucleotide sequence of SEQ ID NO:11 or 13;

(c) a DNA encoding a protein comprising of the amino acid sequence of SEQ ID NO:12 or 14, in which one or more amino acids are modified by substitution, deletion, insertion and/or addition, wherein said protein is functionally equivalent to the protein consisting of the amino acid sequence of SEQ ID NO:12 or 14; and

(d) a DNA hybridizing under stringent conditions with a DNA consisting of the nucleotide sequence of SEQ ID NO:11 or 13, and encoding a protein that is functionally equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:12 or 14;

(2) a DNA encoding a partial peptide of a protein consisting of the amino acid sequence of SEQ ID NO:12 or 14;

(3) a protein or a peptide encoded by the DNA of any one of (1) or (2);

(4) a vector into which the DNA of any one of (1) or (2) is inserted;

(5) a host cell retaining the vector of (4);

(6) a method for producing the proteins or peptides of (3); comprising the step of culturing the host cells of (5), and recovering expressed protein from said host cell or the culture supernatant;

(7) a polynucleotide comprising at least 15 nucleotides that are complementary to a DNA consisting of the nucleotide sequence of SEQ ID NO:11 or 13 or to a complementary strand thereof;

(8) a method of screening for a compound that binds to the protein of (3), comprising the steps of:

(a) contacting a test sample, containing at least one compound, with the protein or partial peptide of (3);

(b) detecting the binding activity between the compound and the protein or partial peptide thereof; and

(c) selecting the compound that has the activity to bind to the protein or partial peptide thereof;

(9) a compound binding to the protein of (3);

(10) the compound of (9), which is an antibody; and

(11) a compound binding to the protein of (3), which may be isolated by the method of (8).

The present invention provides novel proteins involved in primitive hematopoiesis and DNA encoding these proteins. The nucleotide sequence of the full-length cDNA of mouse "YS68" isolated by the present inventors is indicated in SEQ ID NO:11, and the amino acid sequence of the protein encoded by this cDNA is indicated in SEQ ID NO:12. In addition, the nucleotide sequence of the full-length cDNA of human "YS68" isolated by the present inventors is indicated in SEQ ID NO:13, and the amino acid sequence of the protein encoded by this cDNA is indicated in SEQ ID NO:14.

Hematopoietic stem cells contributing to lifelong hematopoiesis are formed by the differentiation of hemangioblasts, the common mother cells of hematocytes and blood vessels. Several transcription factors thought to be important for primitive hematopoiesis have been reported according to recent gene disruption experiments. Not only angiogenesis but also hematopoiesis was not confirmed in mouse with disruption in SCL (Porcher et al., Cell 86:47-57, 1996; Visvader et al., Genes Dev. 12:473-479, 1998). In addition, AML-1 and c-Myb knockout mice did not show abnormalities in angiogenesis, but they completely lacked definitive hematopoiesis (Okuda et al., Cell 84:321-330, 1996; Lin et al., Curr. Top Microbiol. Immunol. 211:79-87, 1996). However, how these transcription factors interact with each other at the stage of primitive hematopoiesis and become involved in determining the fate of cells remains unknown.

The mouse "YS68" gene (SEQ ID NO: 11) identified by the present inventors was isolated by subtracting cDNA derived from embryonic day 13 mouse yolk sac, which is said to lack the hemangioblast, from cDNA derived from embryonic day 9 yolk sac, which is suggested to have a hemangioblast. The isolated "Y568" gene (SEQ ID NO: 11) was expected to encode a protein of 1,265 amino acids, and showed an expression pattern with a high level expression in embryonic day 9 yolk sac followed by a gradual decrease. In addition, an expression of the gene was observed in the AGM region (considered to be the site of hematopoietic stem cell development) from day 10 embryos and in embryonic day 13 livers; the expression then shifted to strong expression at the thymus and spleen of day 16 embryos. Furthermore, expression in these regions considerably diminished in adult mice. Thus, the "Y568" cloned by the present inventors with such an expression pattern in the developmental stage can be considered as a new member of molecules involved in primitive hematopoiesis.

Although "YS68" is expected to be a nuclear protein because it has multiple nuclear transport signals in its C-terminal region, strong expression was observed not only in the nucleus but also around the nucleus in hepatocytes (Example 6). The finding that WD repeats necessary for binding to proteins existed in the N-terminus, and immunoprecipitation caused coprecipitation of multiple proteins (Example 4) suggested that transport of this protein to the nucleus is regulated by interactions with other proteins.

The idea that blood cells develop from the vascular endothelium has existed for a relatively long time, but was actually proven only recently. Jaffredo et al. stained the entire avian blood vessel with fluorescence-labeled LDL and revealed that the stained vascular endothelium differentiated into hematocytes (Jaffredo et al., Development 125:4575-4783, 1998). In addition, Hara et al. found that hemangioblasts can be concentrated by sorting the cells of the AGM region by PCLP-1 (podocalyxin-like protein 1). Localization of hemangioblasts in the vascular endothelium was suggested by the localized PCLP-1 expression in the AGM region in the vascular endothelium (Hara et al., Immunity 11:567-578, 1999). As shown in Example 5, the expression site of YS68 in the AGM region was the same vascular endothelium as PCLP-1. In addition, this expression pattern is the same as those of AML-1 and SCL, both of which are known to be important for primitive hematopoiesis. Considering that expression of YS68 in the hematocyte of CD34 positive cells, which are thought to be a group of relatively immature hematocytes (Example 6), is strong, YS68 is suggested to function in the process of differentiation from hemangioblasts to hematocytes.

The "YS68" proteins of this invention and DNAs encoding the proteins are useful as differentiation markers and as regulating factors of developmental differentiation and the hematopoietic function of hematopoietic stem cells. Additionally, they may be applicable for diagnosis, prevention, and treatment of diseases in which a protein of this invention is involved. In current medicine, means for artificial amplification of hematopoietic stem cells does not exist. Artificial in vitro proliferation of hematopoietic stem cells may be enabled by forced expression of YS68 using a virus vector in hemangioblasts that are the origin of hematopoietic cells, or by administration of cytokines or compounds that induces the expression of YS68. Therefore, YS68 may be applied to medical treatment, as a new alternative to bone marrow transplant.

In addition, many human blood cell tumors, such as myeloid leukemia and lymphoid leukemia, are often caused by abnormalities in transcription factors, and human "YS68" gene of this invention is likely to be one of the causative genes of these diseases. Therefore, human "YS68" may be particularly applied to genetic diagnosis or gene therapy of such diseases. Furthermore, drug development targeting the human "YS68" gene and protein themselves or molecules that regulate them, or molecules or genes that are regulated by the human "YS68" protein may be useful in the treatment and prevention of the above-mentioned diseases.

Furthermore, this invention includes proteins that are functionally equivalent to the "YS68" protein (SEQ ID NO:12 and 14). For example, mutant forms of the "YS68" protein are included in such proteins. The term "functionally equivalent" herein means that the protein of interest has the function of regulating the development and/or differentiation of hematopoietic cells or has the function of interacting with other proteins.

For example, the function of a protein to regulate the development and/or differentiation of hematopoietic cells can be evaluated using as an index the expression characteristics within the hematopoietic tissues, such as those described in Example 2. On the other hand, the function of a protein to

interact with other proteins can be determined, for example, by utilizing immunoprecipitation, such as those described in Example 4.

As a method well known by a person skilled in the art for preparing a protein functionally equivalent to a given protein, methods for introducing mutations into proteins are known. For example, one skilled in the art can prepare proteins functionally equivalent to the "YS68" proteins (SEQ ID NO:12 and 14) by introducing an appropriate mutation in the amino acid sequence of the protein by site-directed mutagenesis (Hashimoto-Gotoh et al., Gene 152:271-275, 1995; Zoller et al., Methods Enzymol. 100:468-500, 1983; Kramer et al., Nucleic Acids Res. 12:9441-9456, 1984; Kramer et al., Methods. Enzymol. 154:350-367, 1987; Kunkel, Proc. Natl. Acad. Sci. USA 82:488-492, 1985; Kunkel, Methods Enzymol. 85:2763-2766, 1988). Mutation of amino acids can occur in nature, too. The proteins of the present invention include those proteins that comprise the amino acid sequences of the "YS68" protein (SEQ ID NO:12 and 14), wherein one or more amino acids are mutated and yet are functionally equivalent to the protein comprising the sequence of "YS68" protein. It is considered that the number of amino acids to be mutated in such a mutant, is generally 100 amino acids or less, preferably 50 amino acids or less, more preferably 20 amino acids or less, and more preferably 5 amino acid or less.

As for the amino acid residue to be mutated, it is preferable that it is mutated into a different amino acid such that the properties of the amino acid side-chain are conserved. Examples of properties of amino acid side chains are, hydrophobic amino acids (A, I, L, M, F, P, W, Y, V), hydrophilic amino acids (R, D, N, C, E, Q, G, H, K, S, T), and amino acids comprising the following side chains: an aliphatic side-chain (G, A, V, L, I, P); a hydroxyl group containing side-chain (S, T, Y); a sulfur atom containing side-chain (C, M); a carboxylic acid and amide containing side-chain (D, N, E, Q); a base containing side-chain (R, K, H); and an aromatic containing side-chain (H, F, Y, W) (The parenthetic letters indicate the one-letter codes of amino acids).

It is well known that a protein having deletion, addition, and/or substitution of one or more amino acid residues in the sequence of a protein can retain the original biological activity (Mark et al., Proc. Natl. Acad. Sci. USA 81:5662-5666, 1984; Zoller et al., Nucleic Acids Res. 10:6487-6500, 1982; Wang et al., Science 224:1431-1433; Dalbadie-McFarland et al., Proc. Natl. Acad. Sci. USA 79:6409-6413, 1982).

The term "substantially pure" as used herein in reference to a given polypeptide means that the polypeptide is substantially free from other biological macromolecules. For example, the substantially pure polypeptide is at least 75%, 80, 85, 95, or 99% pure by dry weight. Purity can be measured by any appropriate standard method known in the art, for example, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

Accordingly, the invention includes a polypeptide having a sequence shown as SEQ ID NO:12 or 14. The invention also includes a polypeptide, or fragment thereof, that differs from the corresponding sequence shown as SEQ ID NO:12 or 14. The polypeptide can differ from the sequence of SEQ ID NO:12 or 14 by having one or more amino acids substituted, deleted, inserted and/or added. For example, the polypeptide can be a fusion protein, having an additional amino acid sequence at the N- or C-terminus of SEQ ID NO:12 or 14. In preferred embodiments, the protein has no more than 50, 30, 20, 10 or 5 amino acids substituted, deleted, inserted and/or added. Preferably, the difference is a difference or change at one or more non-essential residues or one or more conservative amino acid substitutions, as defined above. In one embodiment, the polypeptide includes an amino acid sequence at least about 60% identical to a sequence shown as SEQ ID NO:12 or 14, or a fragment thereof. Preferably, the polypeptide is at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or more identical to SEQ ID NO:12 or 14 and has at least one YS68 activity described herein, e.g., the protein can regulate development or differentiation of hematopoietic cells. Preferred polypeptide fragments of the invention are at least 10%, preferably at least 20%, 30%, 40%, 50%, 60%, 70%, or more, of the length of the sequence shown as SEQ ID NO:12 or 14 and have at least one YS68 activity described herein. Or alternatively, the fragment can be merely an immunogenic fragment.

A fusion protein comprising "YS68" protein is encompassed in the protein, wherein one or more amino acids residues are added to the amino acid sequence of "YS68". Fusion proteins are fusions of the "YS68" protein and other peptides or proteins, and are included in the present invention. Fusion proteins can be made by techniques well known to a person skilled in the art, such as by linking the DNA encoding the "YS68" protein (SEQ ID NO:12 and 14) with DNA encoding other peptides or proteins so as the frames match, inserting this linked DNA into an expression vector, and expressing it in a host. There is no restriction as to the peptides or proteins to be fused to a protein of the present invention.

Known peptides, for example, FLAG (Hopp et al., Biotechnology 6:1204-1210, 1988), 6×His consisting of six His (histidine) residues, 10×His, Influenza agglutinin (HA), human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, and such, can be used as peptides to be fused to a protein of the present invention. Examples of proteins that may be fused to a protein of the present invention are, GST (glutathione-S-transferase), Influenza agglutinin (HA), immunoglobulin constant region, β-galactosidase, MBP (maltose-binding protein), and such. Fusion proteins can be prepared by fusing commercially available DNA encoding these peptides or proteins with a DNA encoding a protein of the present invention and expressing the fused DNA prepared.

Furthermore, a protein, in which multiple amino acid residues have been added to the amino acid sequence of the "YS68" protein, includes a protein encoded by the nucleotide sequence starting from "a" at position 98 to "g" at position 6922 of SEQ ID NO:15 (protein comprising the amino acid sequence, wherein an amino acid sequence comprising "Met-Ala-Ala-Glu-Arg-Arg-Cys-Gly-Ser" (SEQ ID NO:16) is added to the N terminus of the amino acid sequence of SEQ ID NO:14).

In addition, as a method well known to those skilled in the art for preparing proteins that are functionally equivalent to a known protein, methods that utilize hybridization techniques (Sambrook et al., Molecular Cloning 2nd ed., 9.47-9.58, Cold Spring Harbor Lab. Press, 1989) can be mentioned. More specifically, those skilled in the art may readily isolate DNAs having high homology to the DNA sequences (SEQ ID NO:11 and 13) encoding the "YS68" protein, based on the entire DNA sequence or parts thereof, and isolate DNA encoding proteins functionally equivalent to the "YS68" protein from these DNAs. The present invention includes proteins that are functionally equivalent to the "YS68" protein, and which are encoded by DNAs that hybridize under stringent conditions with DNA encoding the "YS68" protein. When isolating a cDNA that has high sequence homology to the DNA encoding the "YS68" protein, it is considered to be preferable to use embryonic stage hematopoietic tissues (for

example, tissues such as the AGM region and yolk sac during early development; and thymus, spleen, and liver during mid to late development).

Hybridization conditions for isolating DNAs encoding proteins that are functionally equivalent to the "YS68" protein can be appropriately selected by those skilled in the art. Conditions for hybridization, for example, may be those with low stringency. Low stringency conditions means that the washing conditions after hybridization are, for example, 42° C., 2×SSC, and 0.1% SDS, or preferably 50° C., 2×SSC, and 0.1% SDS. Examples of hybridization conditions that are more preferable are conditions with high stringency. An example of high stringency conditions is 65° C., 0.1×SSC and 0.1% SDS. Under these conditions, the higher the temperature, the higher the homology of the obtained DNA will be. However, several factors such as temperature and salt concentration can influence the stringency of hybridization and one skilled in the art can appropriately select such factors to accomplish a similar stringency.

In addition, instead of hybridization, DNA encoding functionally equivalent proteins to "YS68" protein can be isolated by gene amplification methods, for example, by polymerase chain reaction (PCR), which uses primers that are synthesized based on sequence information of DNA encoding the "YS68" protein (SEQ ID NO:11 and 13).

A protein that is functionally equivalent to a "YS68" protein, encoded by a DNA that is isolated by such hybridization techniques and gene amplification techniques, will normally have a high amino acid sequence homology to the "YS68" protein (SEQ ID NO:12 and 14). The proteins of this invention also include proteins that are functionally equivalent to a "YS68" protein and at the same time have a high sequence homology to the amino acid sequence of SEQ ID NO:12 or 14. High sequence homology typically means a homology of 30% or more, preferably a homology of 50% or more, more preferably a homology of 70% or more, and even more preferably a homology of 90% or more (for example, homology of 95% or more). To determine the homology of a protein, an algorithm described in the literature (Wilbur et al., Proc. Natl. Acad. Sci. USA 80:726-730, 1983) can be used.

The proteins of this invention may have different amino acid sequences, molecular weights, and isoelectric points, as well as differences in the presence or absence of sugar chains and their forms, depending on the cells or hosts to produce the protein or production method, which will be described later. However, so long as the obtained protein has the same function as the "YS68" protein, it is included in this invention. For example, if a protein of this invention is expressed in a prokaryotic cell such as *E. coli*, a methionine residue will be added to the N terminus of the amino acid sequence of the original protein. The proteins of this invention will also include such proteins.

The proteins of the present invention can be prepared as recombinant proteins or naturally occurring proteins, by methods well known by those skilled in the art. A recombinant DNA can be prepared by inserting a DNA (for example, the DNA comprising the nucleotide sequence of SEQ ID NOs: 11 or 13) which encodes a protein of the present invention into an appropriate vector, collecting the recombinant obtained by introducing the vector into appropriate host cells, obtaining the extract, and purifying by subjecting the extract to chromatography such as ion exchange, reverse, gel filtration, or affinity chromatography in which an antibody against a protein of the present invention is fixed on column or by combining more than one of these columns.

Also when a protein of the present invention is expressed within host cells (for example, animal cells and *E. coli*) as a fusion protein with glutathione-S-transferase protein or as a recombinant protein supplemented with multiple histidines, the expressed recombinant protein can be purified using a glutathione column or nickel column.

After purifying the fusion protein, it is also possible to exclude regions other than the objective protein by cutting with thrombin or factor-Xa as required.

A naturally occurring protein can be isolated by methods known by a person skilled in the art, for example, by using an affinity column in which the antibody binding to a protein of the present invention (described below) is bound against an extract of tissues or cells expressing a protein of the present invention is expressed. An antibody can be a polyclonal or a monoclonal antibody.

The present invention also contains partial peptides of the proteins of the present invention. A partial peptide of the present invention comprises at least 7 amino acids or more, preferably 8 amino acids or more, and more preferably 9 amino acids or more. The partial peptides can be used, for example, for preparing an antibody against a protein of the present invention, screening a compound binding to a protein of the present invention, and for screening accelerators or inhibitors of a protein of the present invention. The partial peptides can be also used as antagonists or a competitive inhibitors against a protein of the present invention.

A partial peptide of the invention can be produced by genetic engineering, known methods of peptide synthesis, or by digesting a protein of the invention with an appropriate peptidase. For peptide synthesis, for example, solid phase synthesis or liquid phase synthesis may be used.

As used herein, an "isolated nucleic acid" is a nucleic acid, the structure of which is not identical to that of any naturally occurring nucleic acid or to that of any fragment of a naturally occurring genomic nucleic acid spanning more than three genes. The term therefore covers, for example, (a) a DNA which has the sequence of part of a naturally occurring genomic DNA molecule but is not flanked by both of the coding sequences that flank that part of the molecule in the genome of the organism in which it naturally occurs; (b) a nucleic acid incorporated into a vector or into the genomic DNA of a prokaryote or eukaryote in a manner such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Specifically excluded from this definition are nucleic acids present in random, uncharacterized mixtures of different DNA molecules, transfected cells, or cell clones, e.g., as these occur in a DNA library such as a cDNA or genomic DNA library.

Accordingly, in one aspect, the invention provides an isolated or purified nucleic acid molecule that encodes a polypeptide described herein or a fragment thereof Preferably, the isolated nucleic acid molecule includes a nucleotide sequence that is at least 60% identical to the nucleotide sequence shown in SEQ ID NO:11 or 13. More preferably, the isolated nucleic acid molecule is at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, identical to the nucleotide sequence shown in SEQ ID NO:11 or 13. In the case of an isolated nucleic acid molecule which is longer than or equivalent in length to the reference sequence, e.g., SEQ ID NO:11 or 13, the comparison is made with the full length of the reference sequence. Where the isolated nucleic acid molecule is shorter that the reference sequence, e.g., shorter than SEQ ID NO:11

or 13, the comparison is made to a segment of the reference sequence of the same length (excluding any loop required by the homology calculation).

As used herein, "% identity" of two amino acid sequences, or of two nucleic acid sequences, is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score=100, wordlength=12. BLAST protein searches are performed with the XBLAST program, score=50, wordlength=3. To obtain gapped alignment for comparison purposes GappedBLAST is utilized as described in Altschul et al. (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and GappedBLAST programs the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention.

A DNA encoding a protein of the present invention can be used for the production of the protein in vivo or in vitro as described above as well as for, for example, application to gene therapy for diseases attributed to genetic abnormality in the gene encoding the protein of the present invention. Any form of the DNA can be used, so long as it encodes a protein of the present invention. Specifically, cDNA synthesized from mRNA, genomic DNA, or chemically synthesized DNA can be used. The present invention includes a DNA comprising a given nucleotide sequence based on degeneracy of genetic codons, as long as it encodes a protein of the present invention.

A DNA of the present invention can be prepared by methods known to those skilled in the art. For example, a DNA of the present invention can be prepared from a cDNA library from cells which express a protein of the present invention by conducting hybridization using a partial sequence of the DNA of the present invention (e.g., SEQ ID NO:11 and 13) as a probe. A cDNA library can be prepared, for example, by the method described in Sambrook et al., Molecular Cloning, Cold Spring Harbor Laboratory Press, 1989, or using commercially available cDNA libraries. A cDNA library can be also prepared by extracting RNA from cells expressing a protein of the present invention, synthesizing cDNA using reverse transcriptase, synthesizing an oligo DNA base on the sequence of the DNA of the present invention (for example, SEQ ID NOs:11 and 13), conducting PCR by using these as primers, and amplifying cDNA encoding the protein of the present invention.

In addition, by sequencing the nucleotides of the obtained cDNA, a translation region encoded by the cDNA can be determined, and the amino acid sequence of a protein of the present invention can be obtained. Moreover, by screening the genomic DNA library using the obtained cDNA as a probe, genomic DNA can be isolated.

More specifically, mRNAs may first be prepared from a cell, tissue, or organ (for example, embryonic stage hematopoietic tissues suchas AGM region and yolk sac of early development; thymus, spleen, and liver of mid to late development) in which a protein of the invention is expressed. Known methods can be used to isolate mRNAs; for instance, total RNA is prepared by the guanidine ultracentrifugation (Chirgwin et al., Biochemistry 18:5294-5299, 1979) or the AGPC method (Chomczynski et al., Anal. Biochem. 162: 156-159, 1987), and mRNA is purified from total RNA using mRNA Purification Kit (Pharmacia) and such. Alternatively, mRNA may be directly purified by QuickPrep mRNA Purification Kit (Pharmacia).

The obtained mRNA is used to synthesize cDNA using reverse transcriptase. A cDNA may be synthesized using kits, such as the AMV Reverse Transcriptase First-strand cDNA Synthesis Kit (Seikagaku Kogyo). Alternatively, a cDNA may be synthesized and amplified following the 5'-RACE method (Frohman et al., Proc. Natl. Acad. Sci. USA 85:8998-9002, 1988; Belyaysky et al., Nucleic Acids Res. 17:2919-2932, 1989) which uses a primer and such, described herein, the 5'-Ampli FINDER RACE Kit (Clontech), and polymerase chain reaction (PCR).

A desired DNA fragment is prepared from the PCR products and ligated with a vector DNA. The recombinant vectors are used to transform *E. coli* and such, and a desired recombinant vector is prepared from a selected colony. The nucleotide sequence of the desired DNA can be verified by conventional methods, such as the dideoxynucleotide chain termination method.

A DNA of the invention may be also designed to have a sequence that is expressed more efficiently by taking into account the frequency of codon usage in the host to be used for expression (Grantham et al., Nucleic Acids Res. 9:43-74, 1981). A DNA of the present invention may be altered by a commercially available kit or a conventional method. For instance, a DNA may be altered by digestion with restriction enzymes, insertion of synthetic oligonucleotides or appropriate DNA fragments, addition of linkers, or insertion of the initiation codon (ATG) and/or the stop codon (TAA, TGA, or TAG).

The DNAs of this invention include a DNA that (a) hybridizes under stringent conditions with a DNA consisting of the nucleotide sequence of SEQ ID NO:11 or 13 and (b) encodes a protein that is functionally equivalent to a protein of this invention mentioned above. Stringent conditions for hybridization can be selected appropriately by those skilled in the art, and those conditions specifically mentioned above may be used. Under these conditions, DNA having higher homology are obtained as the temperature is raised. The above-mentioned DNA to be hybridized is preferably a naturally occurring DNA, for example, a cDNA or chromosomal DNA.

The present invention also provides vectors into which a DNA of the present invention is inserted. The vectors of the present invention are useful to retain a DNA of the present invention in host cell, or to express a protein of the present invention.

When *E. coli* is used as the host cell and a vector is amplified therein to produce a large amount in *E. coli* (e.g., JM109, DH5α, HB101, or XL1Blue), the vector should have an "ori" that may be amplified in *E. coli* and a marker gene for selecting transformed *E. coli* (e.g., a drug-resistance gene selected by a drug (e.g., ampicillin, tetracycline, kanamycin, or chloramphenicol)). For example, the M13-series vectors, the pUC-series vectors, pBR322, pBluescript, pCR-Script, and so on can be used. In addition to the vectors described above, pGEM-T, pDIRECT, and pT7, for example can also be used for subcloning and extracting cDNA. When a vector is used to produce a protein of the present invention, an expression vector is especially useful. For example, an expression vector to be expressed in *E. coli* should have the above characteristics to be amplified in *E. coli*. When *E. coli*, such as JM109, DH5α, HB101, or XL1 Blue, are used as the host cell, the vector should, in addition to the above characteristics, have a promoter so that the vector is copied in the host, for example, the lacZ promoter (Ward et al., Nature 341:544-546, 1989; FASEB J. 6:2422-2427, 1992), the araB promoter (Better et

al., Science 240:1041-1043, 1988), or the T7 promoter and such, that can efficiently express the desired gene in *E. coli*. As such a vector, for example, pGFX-5X-1 (Pharmacia), "QIAexpress system" (Qiagen), pEGFP or pET (in this case, the host is preferably BL21 which expresses T7 RNA polymerase) can be used in addition to the above vectors.

A vector also may contain a signal sequence for polypeptide secretion. As a signal sequence for protein secretion, the pelB signal sequence (Lei et al., J. Bacteriol. 169:4379, 1987) can be used in the case of producing proteins into the periplasm of *E. coli*. For introducing a vector into host cells, for example, the calcium chloride method, and the electroporation method can be used.

Besides *E. coli*, for example, expression vectors derived from mammals (for example, pcDNA3 (Invitrogen) and pEGF-BOS (Nucleic Acids. Res. 18(17):5322, 1990), pEF, pCDM8); expression vectors derived from insect cells (for example, "Bac-to-BAC baculovirus expression system" (GIBCO BRL), pBacPAK8); expression vectors derived from plants (for example pMH1, pMH2); expression vectors derived from animal viruses (for example, pHSV, pMV, pAdexLcw); expression vectors derived from retroviruses (for example, pZIPneo); expression vector derived from yeast (for example, "*Pichia* Expression Kit" (Invitrogen), pNV11, SP-Q01); expression vectors derived from *Bacillus subtilis* (for example, pPL608, pKTH50) can be used as vectors for producing a protein of the present invention.

In order to express a vector in animal cells, such as CHO, COS, or NIH3T3 cells, the vector should have a promoter necessary for expression in such cells, for example, the SV40 promoter (Mulligan et al., Nature 277:108, 1979), the MMLV-LTR promoter, the EF1α promotor (Mizushima et al., Nucleic Acids Res. 18:5322, 1990), or the CMV promoter, and such, and preferably a marker gene for selecting transformants (for example, a drug resistance gene selected by a drug (e.g., neomycin, G418)). Examples of vectors with these characteristics include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, pOp13, and so on.

In addition, for the purpose of stably expressing a gene and amplifying the copy number of the gene in cells, for example, a method wherein a vector comprising the complementary DHFR gene (for example pCHO I) is introduced into CHO cells in which the nuclei acid synthesizing pathway is deleted and amplified by methotrexate (MTX) can be used. On the other hand, in the case of transient expression of a gene, a method wherein a vector (e.g., pcD) comprising replication origin of SV40 is transformed using COS cells comprising the SV40 T antigen expressing gene on chromosomes can be used. The origin used for replication may be those of polyomavirus, adenovirus, bovine papilloma virus (BPV), and the like. In addition, the expression vector may include a selection marker gene for amplification of the gene copies in host cells. Examples of such markers include, but are not limited to, the aminoglycoside transferase (APH) gene, the thymidine kinase (TK) gene, the *E. coli* xanthine-guanine phosphoribosyl transferase (Ecogpt) gene, and the dihydrofolate reductase (dhfr) gene.

On the other hand, a DNA of the present invention can be expressed in vivo in animals, for example, by inserting a DNA of the present invention into an appropriate vector and introducing it in vivo by a conventional method, such as the retrovirus method, the liposome method, the cationic liposome method, and the adenovirus method. By using these methods, gene therapy against diseases attributed to mutation of 'YS68' gene of the present invention can be effected. As a vector, for example, adenovirus vector (for example pAdexlcw), and retrovirus vector (for example, pZIPneo) can be used, but the present invention is not restricted thereto. Common gene manipulation, for example, insertion of a DNA of the present invention to a vector, can be performed according to any standard method (Molecular Cloning, 5.61-5.63). Administration into a living body can be either an ex vivo method, or in vivo method.

The present invention relates to a host cell into which a vector of the present invention has been introduced. The host cell into which a vector of the invention is introduced is not particularly limited. *E. coli* or various animal cells can be used. The host cells of the present invention can be used, for example, as production system for producing or expressing a protein of the present invention. The present invention provides methods of producing a protein of the invention both in vitro or in vivo. For in vitro production, eukaryotic cells or prokaryotic cells can be used as host cells.

Useful eukaryotic cells as host include animal, plant, or fungi cells. As animal cells, mammalian cells, such as CHO (J. Exp. Med. 108:945, 1995), COS, 3T3, myeloma, baby hamster kidney (BHK), HeLa, and Vero cells; amphibian cells, such as *Xenopus* oocytes (Valle et al., Nature 291:340-358, 1981); or insect cells, such as Sf9, Sf21, and Tn5 cells can be used. CHO cells lacking the DHFR gene (dhfr-CHO) (Proc. Natl. Acad. Sci. USA 77:4216-4220, 1980) or CHO K-1 (Proc. Natl. Acad. Sci. USA 60:1275, 1968) may be also used. In animal cells, CHO cells are particularly preferable for mass expression. A vector can be introduced into host cells by, for example, the calcium phosphate method, the DEAE dextran method, the cationic liposome DOTAP (Boehringer Mannheim), the electroporation method, or the lipofection method.

As plant cells, plant cells originating from *Nicotiana tabacum* are known as a protein-production system, and may be used as callus cultures. As fungi cells, yeast cells such as *Saccharomyces*, including *Saccharomyces cerevisiae*, or filamentous fungi such as *Aspergillus*, including *Aspergillus niger*, are known and may be used herein.

Useful prokaryotic cells include bacterial cells, such as *E. coli*, for example, JM109, DH5α, HB101 are known. Regarding others, *Bacillus subtilis* is known.

These host cells are transformed by a desired DNA, and the resulting transformants are cultured in vitro to obtain a protein. Transformants can be cultured using known methods. Culture medium for animal cell, for example, DMEM, MEM, RPMI1640, or IMDM may be used with or without serum supplement such as fetal calf serum (FCS). The pH of the culture medium is preferably between about pH 6 to 8. Such cells are typically cultured at about 30 to 40° C. for about 15 to 200 hr, and the culture medium may be replaced, aerated, or stirred if necessary.

Animal and plant hosts may be used for in vivo production. For example, a desired DNA can be introduced into an animal or plant host. Encoded proteins are produced in vivo, and then recovered. These animal and plant hosts are included in the host cells of the present invention.

Animals to be used for the production systems described above include, but are not limited to, mammals and insects. Mammals, such as goat, porcine, sheep, mouse, and bovine, may be used (Vicki Glaser, SPECTRUM Biotechnology Applications (1993)). Alternatively, the mammals may be transgenic animals.

For instance, a desired DNA may be prepared as a fusion gene with a gene encoding a protein specifically produced into milk, such as goat β casein. DNA fragments comprising a fusion gene having the desired DNA are injected into goat embryos, which are then introduced back to female goats. Proteins are recovered from milk produced by the transgenic

goats (i.e., those born from the goats that had received the modified embryos) or from their offspring. To increase the amount of milk containing the proteins produced by transgenic goats, appropriate hormones may be administered to them (Ebert et al., Bio/Technology 12:699-702, 1994).

Alternatively, insects, such as the silkworm, may be used. A desired DNA inserted into baculovirus can be used to infect silkworms, and a desired protein is then recovered from their body fluid (Susumu et al., Nature 315:592-594, 1985).

As plants, for example, tobacco can be used. In use of tobacco, a desired DNA is inserted into a plant expression vector, such as pMON530, which is then introduced into a bacteria, such as *Agrobacterium tumefaciens*. Then, the bacteria is used to infect tobacco, such as *Nicotiana tabacum*, and a desired polypeptide is recovered from the leaves of the plant (Julian et al., Eur. J. Immunol. 24:131-138, 1994).

A protein of the present invention obtained as above may be isolated from the interior or exterior (e.g. medium) of the cells or hosts, and purified as a substantially pure homogeneous protein. The method for protein isolation and purification is not limited to any specific method; in fact, any standard method may be used. For instance, column chromatography, filter, ultrafiltration, salt precipitation, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis, isoelectric point electrophoresis, dialysis, and recrystallization may be appropriately selected and combined to isolate and purify the protein.

For chromatography, for example, affinity chromatography, ion-exchange chromatography, hydrophobic chromatography, gel filtration, reverse phase chromatography, adsorption chromatography, and such may be used (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed. Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). These chromatographies may be performed by liquid chromatography, such as HPLC and FPLC. Thus, the present invention provides for highly purified proteins, produced by the above methods.

A protein of the present invention may be optionally modified or partially deleted by treating it with an appropriate protein modification enzyme before or after purification. Useful protein modification enzymes include, but are not limited to, trypsin, chymotrypsin, lysylendopeptidase, protein kinase, and glucosidase.

The present invention provides an antibody that binds to a protein of the invention. The antibody of the invention can be used in any form, such as monoclonal or polyclonal antibodies, and includes antiserum obtained by immunizing a rabbit with a protein of the invention, all classes of polyclonal and monoclonal antibodies, human antibodies, and humanized antibodies produced by genetic recombination.

A protein of the invention used as an antigen to obtain an antibody may be derived from any animal species, but is preferably derived from a mammal such as a human, mouse, or rat, or more preferably from a human. A human-derived protein may be obtained from the nucleotide or amino acid sequences disclosed herein.

In the present invention, a protein to be used as an immunization antigen may be a complete protein or a partial peptide of a protein. A partial peptide may be, for example, an amino (N)-terminal or carboxy (C)-terminal fragment of the protein. Herein, "an antibody" is defined as an antibody that specifically reacts with either the full-length or a fragment of a protein.

A gene encoding a protein of the invention or its fragment may be inserted into a known expression vector, which is then used to transform a host cell as described herein. The desired protein or its fragment may be recovered from the exterior or interior of the host cells by any standard method, and may be used as an antigen. Alternatively, cells expressing the protein or their lysates, or a chemically synthesized protein may be used as an antigen. Short peptides are preferably bound with carrier proteins such as bovine serum albumin, ovalbumin, and keyhole limpet hemocyanin to be used as the antigen.

Any mammalian animal may be immunized with the antigen, but preferably the compatibility with parental cells used for cell fusion is taken into account. In general, animals of the orders Rodentia, Lagomorpha, or Primate are used.

Rodents include, for example, mouse, rat, and hamster. Lagomorphs include, for example, rabbit. Primates include, for example, a monkey of catarrhine (old world monkey) such as *Macaca fascicularis*, rhesus monkey, sacred baboon, or chimpanzee.

Methods for immunizing animals against antigens are known in the art. Intraperitoneal injection or subcutaneous injection of antigens is used as a standard method for immunization of mammals. More specifically, antigens may be diluted and suspended in an appropriate amount with phosphate buffered saline (PBS), physiological saline, etc. If desired, the antigen suspension may be mixed with an appropriate amount of a standard adjuvant, such as Freund's complete adjuvant, made into emulsion, and then administered to mammalian animals. Preferably, it is followed by several administrations of antigen mixed with an appropriately amount of Freund's incomplete adjuvant every 4 to 21 days. An appropriate carrier may also be used for immunization. After immunization as above, serum is examined for increase of the amount of desired antibodies by a standard method.

Polyclonal antibodies against a protein of the present invention may be prepared by collecting blood from the immunized mammal examined for the increase of desired antibodies in the serum, and separating serum from the blood by any conventional method. Polyclonal antibodies may be used as serum containing the polyclonal antibodies, or if necessary, a fraction containing the polyclonal antibodies may be isolated from the serum. Immunoglobulin G or M can be prepared by obtaining a fraction which recognizes only a protein of the present invention using an affinity column coupled with the protein of the present invention and further purifying this fraction by using protein A or protein G column.

To prepare monoclonal antibodies, immune cells are collected from the mammal immunized against an antigen and checked for the increased level of desired antibodies in the serum as described above, and are subjected to cell fusion. The immune cells used for cell fusion are preferably obtained from spleen. Other parental cells can be fused with the above immunocyte; for example, preferably myeloma cells of mammalians, and more preferably myeloma cells which acquired the property for selecting fused cells by drugs can be used.

The above immunocyte and myeloma cells can be fused by known methods, for example, the method by Milstein et al. (Galfre et al., Methods Enzymol. 73:3-46, 1981).

Resulting hybridomas obtained by the cell fusion may be selected by cultivating them in a standard selection medium, such as the HAT medium (medium containing hypoxanthine, aminopterin, and thymidine). The cell culture is typically continued in the HAT medium for several days to several weeks, a sufficient time to allow all the other cells, except desired hybridoma (non-fused cells), to die. Then, by the standard limiting dilution method, a hybridoma cell producing the desired antibody is screened and cloned.

In addition to the above method, in which a non human animal is immunized against an antigen for preparing hybridoma, human lymphocytes, such as that infected by EB virus,

may be immunized with a protein, protein expressing cells, or their lysates in vitro. Then, the immunized lymphocytes are fused with human-derived myeloma cells capable of indefinitely dividing, such as U266, to yield a hybridoma producing a desired human antibody having binding ability to the protein can be obtained (Unexamined Published Japanese Patent Application (JP-A) No. Sho 63-17688).

Next, the monoclonal antibody, obtained by transplanting the obtained hybridomas into the abdominal cavity of a mouse and by extracting ascites, can be purified by, for example, ammonium sulfate precipitation, protein A or protein G column, DEAE ion exchange chromatography, or an affinity column to which a protein of the present invention is coupled. An antibody of the present invention can be used not only for purification and detection of a protein of the present invention, but also as a candidate for agonists and antagonists of a protein of the present invention. In addition, an antibody can be applied to antibody treatment for diseases associated with a protein of the present invention. When the obtained antibody is used for the administration to the human body (antibody treatment), a human antibody or a humanized antibody is preferable for reducing immunogenicity.

For example, transgenic animals having a repertory of human antibody genes may be immunized against a protein, protein expressing cells, or their lysates as an antigen. Antibody producing cells are collected from the animals, and fused with myeloma cells to obtain hybridoma, from which human antibodies against a protein can be prepared (see WO92-03918, WO93-2227, WO94-02602, WO94-25585, WO96-33735, and WO96-34096).

Alternatively, an immune cell, such as an immunized lymphocyte, producing antibodies may be immortalized by an oncogene and used for preparing monoclonal antibodies.

Monoclonal antibodies thus obtained can be also recombinantly prepared using genetic engineering techniques (see, for example, Borrebaeck C. A. K. and Larrick, J. W., THERAPEUTIC MONOCLONAL ANTIBODIES, published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). A DNA encoding an antibody may be cloned from an immune cell, such as a hybridoma or an immunized lymphocyte producing the antibody, inserted into an appropriate vector, and introduced into host cells to prepare a recombinant antibody. The present invention also provides recombinant antibodies prepared as described above.

Furthermore, an antibody of the present invention may be a fragment of an antibody or modified antibody, so long as it binds to one or more of the proteins of the invention. For instance, the antibody fragment may be Fab, $F(ab')_2$, Fv, or single chain Fv (scFv), in which Fv fragments from H and L chains are ligated by an appropriate linker (Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883, 1988). More specifically, an antibody fragment may be generated by treating an antibody with enzymes such as papain or pepsin. Alternatively, a gene encoding an antibody fragment may be constructed, inserted into an expression vector, and expressed in an appropriate host cell (see, for example, Co et al., J. Immunol. 152:2968-2976, 1994; Better et al., Methods Enzymol. 178:476-496, 1989; Pluckthun et al., Methods Enzymol. 178: 497-515, 1989; Lamoyi, Methods Enzymol. 121:652-663, 1986; Rousseaux et al., Methods Enzymol. 121:663-669, 1986; Bird et al., Trends Biotechnol. 9:132-137, 1991).

An antibody may be modified by conjugation with a variety of molecules, such as polyethylene glycol (PEG). The present invention provides such modified antibodies. The modified antibody can be obtained by chemically modifying an antibody. These modification methods are conventional in this field.

Alternatively, an antibody of the present invention may be obtained as a chimeric antibody, between a variable region derived from nonhuman antibody and the constant region derived from human antibody; or as a humanized antibody, comprising the complementarity determining region (CDR) derived from nonhuman antibody, the frame work region (FR) derived from human antibody, and the constant region.

Obtained antibodies may be purified into homogeneity. An antibody used in the present invention can be separated and purified by conventional methods used for separating and purifying usual proteins. For example, the separation and purification of a protein can be performed by an appropriately selected and combined use of column chromatography, such as affinity chromatography, filter, ultrafiltration, salting-out, dialysis, SDS polyacrylamide gel electrophoresis, isoelectric focusing, and others (Antibodies: A Laboratory Manual. Ed Harlow and David Lane, Cold Spring Harbor Laboratory, 1988); however, the present invention is not limited thereto. The concentration of antibodies obtained above can be determined by measuring absorbance, by the enzyme-linked immunosorbent assay (ELISA), and so on.

Examples of columns used for affinity chromatography include protein A columns and protein G columns. Examples of columns using protein A column include Hyper D, POROS, Sepharose F. F. (Pharmacia), etc.

In addition to affinity chromatography, the chromatography includes, for example, ion-exchange chromatography, hydrophobic chromatography, gel filtration, reverse-phase chromatography, adsorption chromatography, and the like (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). The chromatographic procedures can be carried out by liquid-phase chromatography such as HPLC, FPLC, or the like.

For example, measurement of absorbance, enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), radioimmunoassay (RIA), and/or immunofluorescence may be used to measure the antigen binding activity of an antibody of the invention. In ELISA, an antibody of the present invention is immobilized on a plate, a protein of the invention is applied to the plate, and then a sample containing a desired antibody, such as culture supernatant of antibody producing cells or purified antibodies, is applied. Then, a secondary antibody that recognizes the primary antibody and is labeled with an enzyme, such as alkaline phosphatase, is applied, and the plate is incubated. Next, after washing, an enzyme substrate, such as p-nitrophenyl phosphate, is added to the plate, and the absorbance is measured to evaluate the antigen binding activity of the sample. A fragment of a protein, such as a C-terminal fragment, may be used as a protein. BIAcore (Pharmacia) may be used to evaluate the activity of an antibody according to the present invention.

The above methods allow for the detection or measurement of the proteins of the invention, by exposing an antibody of the invention to a sample assumed to contain a protein of the invention, and detecting or measuring the immune complex formed by the antibody and the protein. Because the method of detection or measurement of proteins according to the invention can specifically detect or measure proteins, the method may be useful in a variety of experiments in which the protein is used.

The present invention provides a polynucleotide having at least 15 nucleotides that is complementary to the DNA that encodes the "YS68" protein (SEQ ID NO:11 or 13) or the complementary strand thereof.

Herein, the term "complementary strand" is defined as one strand of a double strand DNA composed of A:T and G:C base

pairs to the other strand. In addition, "complementary" is defined as not only those completely matching within a continuous region of at least 15 nucleotides, but also having a homology of at least 70%, preferably at least 80%, more preferably 90%, and even more preferably 95% or higher within that region. The homology may be determined using the algorithm described herein.

Probes or primers for detection and amplification of a DNA encoding a protein of this invention, or nucleotides or nucleotide derivatives for suppressing protein expression (for example, antisense oligonucleotides and ribozymes, or DNA encoding them) are included in these polynucleotides. In addition, such polynucleotides may be also used for preparing DNA chips.

When used as a primer, the region on the 3' side is designed to be complementary to a DNA encoding a protein of the invention, and restriction enzyme recognition sequence and tags can be added to the 5' side.

For example, an antisense oligonucleotide that hybridizes with a portion of the nucleotide sequence of SEQ ID NO:11 or 13 is also included in the antisense oligonucleotides of the present invention. An antisense oligonucleotide is preferably one against at least 15 continuous nucleotides in the nucleotide sequence of SEQ ID NO:11 or 13. More preferably, it is an antisense oligonucleotide having at least 15 continuous nucleotides that contains the translation initiation codon.

Derivatives or modified products of antisense oligonucleotides can be used as antisense oligonucleotides. Examples of such modified products are, lower alkyl phosphonate modifications such as methyl-phosphonate-type or ethyl-phosphonate-type, phosphothioate modifications and phosphoamidate modifications.

The term "antisense oligonucleotides" as used herein means, not only those in which the entire nucleotides corresponding to those constituting a specified region of a DNA or mRNA are complementary, but also those having a mismatch of one or more nucleotides, so long as DNA or mRNA and an oligonucleotide can specifically hybridize with the nucleotide sequence of SEQ ID NO:11 or 13.

An antisense oligonucleotide derivative of the present invention has inhibitory effect on the function of a protein of the present invention as a result that the derivative inhibits the expression of the protein of the invention by acting upon cells producing the protein of the invention and by binding to the DNA or mRNA encoding the protein to inhibit its transcription or translation or to promote the degradation of the mRNA.

An antisense oligonucleotide derivative of the present invention can be made into an external preparation, such as a liniment and a poultice, by mixing with a suitable base material which is inactive against the derivatives.

Also, as necessary, the derivatives can be formulated into tablets, powders, granules, capsules, liposome capsules, injections, solutions, nose-drops, and freeze-drying agents and such by adding excipients, isotonic agents, solubilizing agents, stabilizers, preservative substance, pain-killers, and such. These can be prepared by following usual methods.

An antisense oligonucleotide derivative is given to a patient by directly applying onto the ailing site or by injecting into a blood vessel so that it will reach the site of ailment. An antisense-mounting medium can also be used to increase durability and membrane-permeability. Examples are, liposome, poly-L-lysine, lipid, cholesterol, lipofectin or derivatives of these.

The dosage of an antisense oligonucleotide derivative of the present invention can be adjusted suitably according to the patient's condition and used in desired amounts. For example, a dose range of 0.1 to 100 mg/kg, preferably 0.1 to 50 mg/kg can be administered.

An antisense oligonucleotide of the invention inhibits the expression of a protein of the invention and thereby is useful for suppressing the biological activity of the protein of the invention. Also, expression-inhibitors comprising an antisense oligonucleotide of the invention are useful in that they can inhibit the biological activity of a protein of the invention. It is thought that it is possible to use an antisense oligonucleotides of this invention for the purpose of suppressing biological activities of a protein of the invention.

A protein of the invention may be used for screening compounds binding to the protein. Specifically, a protein may be used in methods of screening for compounds comprising the steps of: (1) exposing a protein of the present invention to a test sample in which a compound binding to the protein is expected to be contained; (2) detecting the binding activity of the protein to the test sample; and (3) selecting the compound having the binding activity to the protein.

A protein of the present invention to be used for screening may be a recombinant protein, a protein derived from the nature, or partial peptide thereof. Alternatively, the protein may be in a form expressed on a cell surface or in a form of cell membrane fraction. Any test sample, for example, cell extracts, cell culture supernatant, products of fermenting microorganism, extracts from marine organism, plant extracts, purified or crude proteins, peptides, non-peptide compounds, synthetic low molecular compounds and naturally occurring compounds, can be used. A protein of the present invention to be contacted with a test sample can be contacted, for example, as a purified protein, a soluble protein, a form bound to a carrier, a fusion protein with another protein, a form expressed on cell membrane, or a cell membrane fraction.

By using a protein of the present invention, for example, in a method for screening for proteins binding to the protein thereof, many methods well known by a person skilled in the art can be used. Such a screening can be conducted by, for example, the immunoprecipitation method, specifically, in the following manner. A gene encoding a protein of the present invention is expressed in a host cell, such as an animal cell, by inserting the gene into an expression vector for foreign gene, such as pSV2neo, pcDNA I, pCD8. As a promoter to be used for the expression, any promoter which can be generally used can be selected; for example, the SV40 early promoter (Rigby in Williamson (ed.), Genetic engineering, vol. 3. Academic Press, London, p. 83-141, 1982), the EF-1α promoter (Kim et al., Gene 91:217-223, 1990), the CAG promoter (Niwa et al., Gene 108:193-200, 1991), the RSV LTR promoter (Cullen Methods in Enzymology 152:684-704, 1987), the SRα promoter (Takebe et al., Mol. Cell. Biol. 8:466, 1988), the CMV immediate early promoter (Seed et al., Proc. Natl. Acad. Sci. USA 84:3365-3369, 1987), the SV40 late promoter (Gheysen et al., J. Mol. Appl. Genet. 1:385-394, 1982), the Adenovirus late promoter (Kaufman et al., Mol. Cell. Biol. 9:946, 1989), the HSV TK promoter, and so on may be used.

To express a foreign gene by introducing the gene into animal cells, the electroporation method (Chu et al., Nucl. Acid Res. 15:1311-1326, 1987), the calcium phosphate method (Chen et al., Mol Cell. Biol. 7:2745-2752, 1987), the DEAE dextran method (Lopata et al., Nucl. Acids Res. 12:5707-5717, 1984; Sussman et al., Mol. Cell. Biol. 4:1642-1643, 1985), the Lipofectin method (Derijard, Cell 7:1025-1037, 1994; Lamb et al., Nature Genetics 5:22-30, 1993;

Rabindran et al., Science 259:230-234, 1993), and such can be exemplified, and any method can be used.

A protein of the present invention can be expressed as a fusion protein comprising a recognition site (epitope) of a monoclonal antibody by introducing the epitope of the monoclonal antibody, whose property has been revealed, to N or C terminus of the protein of the present invention. A commercially available epitope-antibody system can be used (Experimental Med. 13:85-90, 1995). Through a multiple cloning site, a vector which can express a fusion protein with, for example, β-galactosidase, maltose binding protein, glutathione S-transferase, green florescence protein (GFP), is available in the market.

Methods have been reported in which fusion proteins are prepared by introducing only small epitopes comprising several to a dozen of amino acids, so that the properties of the proteins of the present invention may not change by making the proteins fusion proteins. Epitopes, for example, polyhistidine (His-tag), influenza aggregate HA, human c-myc, FLAG, Vesicular stomatitis virus glycoprotein (VSV-GP), T7 gene 10 protein (T7-tag), human simple herpes virus glycoprotein (HSV-tag), epitope such as E-tag (an epitope on monoclonal phage), and monoclonal antibodies recognizing these can be used as an epitope-antibody system for screening a protein binding to a protein of the present invention (Experimental Med. 13:85-90, 1995).

In the immunoprecipitation, an immune complex is formed by adding these antibodies to cell eluate prepared by using an appropriate detergent. This immune complex comprises a protein of the present invention, a protein having a binding affinity for the protein, and an antibody. Immunoprecipitation can be conducted by an antibody against a protein of the present invention, besides using antibodies against the above epitopes. An antibody against a protein of the present invention can be prepared, for example, by introducing a gene encoding the protein of the present invention into an appropriate *E. coli* expression vector; expressing the gene in *E. coli*; purifying the expressed protein; and immunizing animals, for example, rabbits, mice, rats, goats, domestic fowls, and such, with such protein. The antibody can be prepared also by immunizing the above animals against a synthesized partial peptide of a protein of the present invention.

An immune complex can be precipitated, for example, by Protein A Sepharose or Protein G Sepharose when the antibody is mouse IgG antibody. When a protein of the present invention is prepared as a fusion protein with an epitope, for example GST, an immune complex can be formed by using a substance specifically binding to these epitopes, such as glutathione-Sepharose 4B, in the same manner as in the use of an antibody against a protein of the present invention.

Popular Immunoprecipitation can be performed by following or according to, for example, the reference (Harlow, E. and Lane, D.: Antibodies pp. 511-552, Cold Spring Harbor Laboratory publications, New York (1988)).

SDS-PAGE is commonly used for analysis of immunoprecipitated proteins and the binding protein can be analyzed depending on the molecular weight of the protein by using gel with an appropriate concentration. In general, because it is difficult to detect a protein binding to a protein of the present invention by a common staining method, such as Coomassie staining or silver staining, the detection sensitivity for the protein can be improved by culturing in a culture medium containing radioactive isomer, ^{35}S-methionine or ^{35}S-cystein, labeling proteins in the cells, and detecting the proteins. The target protein can be purified from the SDS-polyacrylamide gel and its sequence can be determined directly after the molecular weight of the protein is determined.

The present inventors have detected multiple proteins that bind to a protein of this invention by immunoprecipitation in the Example (Example 4).

To isolate proteins that bind to a protein of the present invention by using the protein, for example, West western blotting (Skolnik et al., Cell 65:83-90, 1991) may be used. More specifically, it is conducted as follows: (1) constructing a cDNA library using a phage vector (λgt11, ZAP, etc.) from cells, tissues, and organs (for example, AGM region and yolk sac during early development; thymus, spleen, and liver during mid to late development, and such) that are expected to express binding proteins that bind to the protein of this invention; (2) expressing the cDNA library on LB-agarose and immobilizing the expressed protein onto a filter; (3) reacting the purified and labeled protein of this invention with the filter; and (4) detecting the plaque expressing the protein that binds to the protein of this invention by the label. Methods to label a protein of this invention may be a method that utilizes the binding characteristics of biotin and avidin; a method utilizing antibodies that bind specifically to the protein of this invention or to peptides or polypeptides fused to the protein of this invention (for example GST and such); a method that utilizes radioisotopes; a method that utilizes fluorescence; and such.

Further, another embodiment of the screening method of this invention is exemplified by a method utilizing the two-hybrid system using cells (Fields et al., Trends. Genet. 10:286-292, 1994; Dalton et al., Cell 68:597-612; "MATCHMAKER Two-Hybrid System", "Mammalian MATCHMAKER Two-Hybrid Assay Kit", "MATCHMAKER One-Hybrid System" (all manufactured by Clonetech); and "HybriZAP Two-Hybrid Vector System" (manufactured by Stratagene)). In the two-hybrid system, a protein of this invention or a partial peptide thereof may be fused to the DNA binding region of SRF or GAL4, and expressed in yeast. A cDNA library is constructed from cells predicted to express proteins that bind to the protein of this invention, wherein the cDNA library is constructed in such a way that the proteins are expressed as fusion proteins with transcription activation regions of VP16 or GAL4. The cDNA library is transfected into the above yeast, and then positive clones are detected to isolate the cDNA derived from the library (expression of a protein that binds to the protein of the invention in yeast leads to the binding of the two proteins, and results in the activation of the reporter gene, which allows to detect positive clones). The protein encoded by the isolated cDNA may be obtained by introducing the cDNA into *E. coli* and expressing it therein. Thus, it is possible to prepare proteins that bind to a protein of this invention and genes encoding them. The reporter gene used in the two-hybrid system may be such as Ade2 gene, Lac Z gene, CAT gene, luciferase gene, PAI-1 (Plasminogen activator inhibitor type 1) gene, and such besides HIS3 gene, but are not limited to these examples.

A protein binding to a protein of the present invention can be screened using affinity chromatography. For example, a preferred method for screening of the present invention utilizes affinity chromatography. A protein of the invention is immobilized on a carrier of an affinity column, and a test sample, in which a protein capable of binding to the protein of the invention is supposed to be expressed, is applied to the column. A test sample herein may be, for example, cell extracts, cell lysates, etc. After loading the test sample, the column is washed, and proteins bound to the protein of the invention can be prepared.

The amino acid sequence of the obtained protein is analyzed, an oligo DNA was synthesized based on the sequence,

and cDNA libraries are screened using the DNA as a probe to obtain a DNA encoding the protein.

A biosensor using the Surface Plasmon Resonance phenomenon may be used as a means for detecting or quantifying the bound compound in the present invention. When such a biosensor is used, the interaction between a protein of the invention and a test compound can be observed in real-time as a surface plasmon resonance signal, using only a minute amount of proteins without labeling (for example, BIAcore, Pharmacia). Therefore, it is possible to evaluate the binding between a protein of the invention and a test compound using a biosensor such as BIAcore.

Methods of screening molecules that bind when an immobilized protein of the present invention is exposed to synthetic chemical compounds, natural substance banks, or a random phage peptide display library, and methods of screening using high-throughput based on combinatorial chemistry techniques (Wrighton et al., Science 273:458-64, 1996; Verdine, Nature 384:11-13, 1996; Hogan, Jr., Nature 384:17-9, 1996) are well known to those skilled in the art as methods for isolating not only proteins but also chemical compounds that bind to a protein of the present invention (including agonist and antagonist).

Compounds that bind to a protein of this invention serve as drug candidates for promoting or inhibiting the activity of the protein of this invention, and may be applied to treatment of diseases caused by expressional or functional abnormalities of the protein of this invention, or diseases that may be treated by regulating the activity of the protein of this invention. Compounds obtained by using the screening method of this invention, wherein the structure of compounds having binding activity toward a protein of this invention is partially altered by addition, deletion, and/or replacement, are also included as compounds that bind to a protein of this invention.

When a compound binding to a protein of the present invention is used as a pharmaceutical for humans and other mammals, such as, mice, rats, guinea pigs, rabbits, chicken, cats, dogs, sheep, pigs, bovines, monkeys, baboons, chimpanzees, the isolated compound can be administered not only directly, but also as dosage forms using known pharmaceutical preparation methods. For example, according to the need, the drugs can be taken orally as sugarcoated tablets, capsules, elixirs and microcapsules; or non-orally in the form of injections of sterile solutions or suspensions with water or any other pharmaceutically acceptable liquid. For example, the compounds can be mixed with pharmacologically acceptable carriers or medium, specifically, sterilized water, physiological saline, plant-oil, emulsifiers, suspending agent, surface-active agent, stabilizers, flavoring agents, excipients, vehicles, preservatives and binders, into a unit dose form required for generally accepted drug implementation. The amount of active ingredient in these preparations makes a suitable dosage within the indicated range acquirable.

Examples of additives which can be mixed to tablets and capsules are, binders such as gelatin, corn starch, tragacanth gum and gum acacia; excipients such as crystalline cellulose; swelling agents such as corn starch, gelatin and alginic acid; lubricants such as magnesium stearate; sweeteners such as sucrose, lactose or saccharin; flavoring agents such as peppermint, *Gaultheria adenothrix* oil and cherry. When the unit dosage form is a capsule, a liquid carrier such as oil can also be included in the above ingredients. Sterile composites for injection can be formulated following normal drug implementations using vehicles such as distilled water used for injections.

Physiological saline, glucose, and other isotonic liquids including adjuvants, such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride, can be used as aqueous solutions for injections. These can be used in conjunction with suitable solubilizers, such as alcohol, specifically ethanol; polyalcohols such as propylene glycol and polyethylene glycol; and non-ionic surfactants such as Polysorbate 80™ and HCO-50.

Sesame oil or Soy-bean oil can be used as a oleaginous liquid and may be used in conjunction with benzyl benzoate or benzyl alcohol as solubilizers; they further may be formulated with a buffer such as phosphate buffer and sodium acetate buffer, a pain-killer such as procaine hydrochloride, a stabilizer such as benzyl alcohol and phenol, and an antioxidant. The prepared injection may be filled into a suitable ampule.

Methods well known to one skilled in the art may be used to administer the pharmaceutical compounds of the present invention to patients, for example as intraarterial, intravenous, percutaneous injections and also as intranasal, transbronchial, intramuscular percutaneous, or oral administrations. The dosage varies according to the body-weight and age of a patient and the administration method, but one skilled in the art can suitably select them. If the compound can be encoded by a DNA, the DNA can be inserted into a vector for gene therapy to perform the therapy. The dosage and method of administration vary according to the body-weight, age, and symptoms of a patient, but one skilled in the art can select them suitably.

Although there are some differences according to the symptoms, the dose of a compound that binds with a transcriptional regulatory factor of the present invention and inhibits its activity is about 0.1 mg to about 100 mg per day, preferably about 1.0 mg to about 50 mg per day and more preferably about 1.0 mg to about 20 mg per day, when administered orally to a normal adult (weight 60 kg).

When administering parenterally in the form of an injection to a normal adult (weight 60 kg), although there are some differences according to the patient, target organ, symptoms and method of administration, it is convenient to intravenously inject a dose of about 0.01 mg to about 30 mg per day, preferably about 0.1 to about 20 mg per day and more preferably about 0.1 to about 10 mg per day. Also, in the case of other animals too, it is possible to administer an amount converted to 60 kgs of body-weight or an amount converted to body surface.

All publications and patents cited herein are incorporated by reference in their entirety.

DESCRIPTION OF DRAWINGS

FIG. **1** depicts photomicrographs indicating the localization of YS68 within cells. YS68 tagged with a flag epitope is expressed in COS7 cells, and upon staining with anti-Flag antibodies, the expression sites of YS68 were investigated (right). In addition, the same cells were treated with Hoechst to selectively stain the nucleus (left).

FIG. **2** depicts photographs demonstrating the result of electrophoresis showing the expression distribution of YS68 in tissues. RNA was prepared from liver, thymus, or spleen tissues of an embryonic day 14 (E14) or embryonic day 18 (E18) mouse embryo, respectively, or from the tissues of an adult mouse to perform Northern hybridization. The lower panel shows 18S ribosomal RNA before blotting as a control.

FIG. **3** depicts photographs demonstrating the result of electrophoresis showing the result of analyzing YS68 expression by RT-PCR in the yolk sac at each stage of a developing embryo.

FIG. **4** depicts photographs demonstrating the result of electrophoresis showing the result of analyzing YS68 expres-

sion by RT-PCR in the AGM region at each stage of a developing embryo is shown in (A); and in (B) the E10.5 AGM region was cultivated in the presence or absence of oncostatin M (OSM), and RNA was prepared on the 5th day of cultivation. Expression of YS 68 was then compared to those of uncultivated AGM region by RT-PCR.

FIG. **5** depicts photographs demonstrating the result of electrophoresis showing the result of comparison of the expression level of YS68 by RT-PCR upon extraction of RNA from liver, thymus and spleen of embryonic (E11.5 to E16.5), 7-day-old, and adult mice, respectively.

FIG. **6** depicts photographs showing the result of in situ hybridization on slices prepared from an E11.5 embryo. A is an autoradiogram, and B is an image obtained by staining the same slice by hematoxylin. Li: liver.

FIG. **7** depicts photographs showing the result of in situ hybridization on slices prepared from an E14.5 embryo. A and C are autoradiograms, while B and D are images obtained by staining the same slices by hematoxylin. Li: liver, Lu: lung, Th: thymus, and N: neural tube.

FIG. **8** depicts a comparison of the amino acid sequences between human (SEQ ID NO: 14) and mouse YS68 fSEQ ID NO: 12).

FIG. **9** depicts the comparison of the amino acid structures of human and mouse YS68.

FIG. **10** depicts a photograph showing the result of analysis on proteins that coprecipitate with YS68. After primary cultivation of E14.5 liver, cell lysate was prepared. Then, the lysate was subjected to immunoprecipitation with anti-YS68 antibody and protein A (Lane 1), rabbit IgG and protein A (Lane 2), and protein A alone (Lane 3). Following SDS-PAGE, the gel was visualized by silver staining. Arrow: YS68; and *: protein that coprecipitated with YS68.

FIG. **11** depicts photographs showing the result of immunostaining of YS68 in tissues. The dorsal aorta (A, B, C, D, and E), the umbilical artery (F) of an E11.5 mouse; and the blood vessels within an E9 yolk sac (H) were stained with erythroid marker TER119 (A, B, and G) and with anti-YS68 antibody (C, D, E, and H). B and D are enlargements of A and C, respectively, and E shows a different view of the aorta. The site where the hematocyte is budding from the vascular endothelium is indicated by an arrow.

FIG. **12** depicts photographs showing the result of staining primary culture cells of E14.5 liver with anti-YS68 antibodies (A), or with rabbit IgG (B). The expression of YS68 was strong at the nucleus and around the nucleus.

FIG. **13** depicts photographs showing the result of investigation on the expression of YS68 in hematocytes isolated from E14 liver. The Giemsa stained hematocytes of the liver (A); hematocytes of the E14.5 liver (B); CD34 negative cells (C); and CD34 positive cells (D) were stained with anti-YS68 antibodies. Whether the sorted cells are CD34 positive or not was confirmed (E-H). E-F and G-H are taken from the same views, E and G are fluorescence photographs, and F and H are visual photographs. Most of the cells sorted by CD34 were weakly CD34 positive to strongly positive (E and F). Cells that passed through the CD34 column were hardly expressing any CD34 (G and H).

FIG. **14** depicts photographs showing the localization of YS68 within cells. A slightly magnified photograph is shown on the left, and a largely magnified photograph is shown on the right. Cells derived from fetal liver were stained with anti-YS68 antibodies to investigate endogenous expression sites of YS68 (top row). In addition, pEFBOSE-F-YS68 (5-1148) that expresses the N-terminal region of YS68 (middle row), or pEFBOSE-F-YS68 (981-2243) that expresses the C-terminal region of YS68 (bottom row) were transfected to COS7 cells, and these cells were stained with anti-Flag antigens to investigate the localization within the cell.

DETAILED DESCRIPTION

The present invention will be described specifically by way of examples below, however this invention is not restricted in any way to these examples.

Example 1

Isolation of YS68 Gene

To obtain molecules that are expressed specifically in hemangioblasts, an experiment was carried out in which cDNA of an E14 yolk sac was subtracted from the cDNA of an E9 yolk sac. Poly A RNAs were purified from each of the E9 and E14 yolk sacs, respectively; then PCR-Select cDNA Subtraction Kit (Clonetech) was used for the subtraction. The obtained cDNA fragments were subcloned into pGEM-T vectors (Promega), and then, after selecting highly expressed cDNAs in E9 yolk sacs by dot blotting, selected cDNA were sequenced. The clone #68 was a novel gene fragment that was not registered in the database. Thus, a primer was designed from the sequence of this gene fragment, and using mouse 15-day Embryo Marathon-Ready cDNA (Clonetech) as a template, a full-length cDNA was isolated by the 5'-RACE method. Mouse YS68 encodes 1,265 amino acids, but is expected to have further upstream sequence.

The obtained YS68 did not have a characteristic motif within its amino acid sequence. However, existence of multiple nuclear transport signals was confirmed. Consequently, YS68 was anticipated to be a protein that functions in the nucleus. Therefore, to confirm the hypothesis, a vector (pEFBOSE-Flag (Nakashima et al., FEBS Let. 403:79-82, 1997) that expresses the mouse YS68 protein (1265 amino acids) tagged with Flag was transfected to COS7 cells. After 24 hours, the cells were fixed with 4% formalin, and was treated with 0.1% Triton-X 100. Then, this was reacted with anti-Flag antibodies, followed by FITC-labeled anti-mouse IgG, and was observed through a fluorescence microscope. Consequently, expression of YS68 was strong in the nucleus, as expected (FIG. **1**). Since the cell nucleus is the site where DNA transcription occurs, YS68 is anticipated to be a transcription factor involved with DNA transcription.

Human YS68 gene was isolated by 5'-RACE and 3'-RACE by designing a primer based on the genetic sequence of mouse YS68. More specifically, based on the genetic sequence of mouse YS68, EST fragments that are thought to be YS68 homologues in humans were searched in the EST database. Primers were designed based on this EST fragment, and using human fetal liver Marathon-Ready cDNA (Clonetech) as a template, the 5' region and the 3' region cDNA were isolated by 5'-RACE and 3'-RACE according to the instructed procedure. The isolated cDNA nucleotide sequence is described in SEQ ID NO:11, and the amino acid sequence of the protein encoded by this cDNA is described in SEQ ID NO:12. A comparison of human and mouse YS68 amino acid sequences is shown in FIG. **8**.

Example 2

Expression Pattern Analysis of YS68

The expression distribution of YS68 within tissues was analyzed by Northern blotting. Total RNA was prepared from

each tissues of embryonic or adult mice using ISOGEN (Wako). 25 μg/lane of these samples were electrophoresed. After blotting onto a nylon membrane, hybridization was performed with YS68 cDNA fragments labeled with ^{32}P. Hybridization was performed in ExpressHyb solution (Clonetech) at 68° C. for 2 hours; then, after several washings with 2×SSC and 0.1% SDS at room temperature, followed by several washings with 0.1×SSC and 0.1% SDS at 65° C., autoradiography was performed.

The expression of YS68 in adult tissue was the strongest in testis, followed those in kidney and lung. Observation of YS68 expression in hematopoietic tissues showed that expression was very strong in liver, thymus and spleen that function as hematopoietic tissues during the embryonic stage. However, expression in these tissues rapidly decreased or was absent in those of adult (FIG. **2**).

Further, the expression pattern in tissues known to be involved in primitive hematopoiesis was investigated in detail. The site of hematopoiesis is known to shift during the embryonic stage as described below from previous studies. First, primitive hematopoiesis starts in the yolk sac at E8, and definitive hematopoiesis begins later in the AGM region at E10.5. Hematocytes that developed in AGM are immediately transported to liver that is formed around E11.5, then differentiate and proliferate at this site until immediately after birth. Meanwhile, hematopoiesis begins to take place in thymus and spleen that are formed around E16.5. After birth, the site of hematopoiesis changes to bone marrow. Based on these facts, the expression pattern of YS68 in these tissues was analyzed in further detail by RT-PCR. Total RNA was extracted from each tissue of mouse embryos at each developmental stage, or an adult mouse; and 1 μg of each total RNA was reverse transcribed to cDNA using SUPERSCRIPT II preamplification system (Gibco). This was used as a template and a YS68-specific primer (68•3: 5'-CACCCGTGAAGAAACAAAT-AGGCA-3'/SEQ ID NO:3, 68•4: 5'-CCTTTGGTACATGAGCTTCTATTT-5'/SEQ ID NO:4) or a G3PDH-specific primer was used to perform PCR (25 cycles of 94° C. for 30 seconds, 62° C. for 30 seconds, and 72° C. for 30 seconds). Then was electrophoresed on 1% agarose gel, and the gel was stained with ethidium bromide.

Expression of YS68 decreased gradually in the yolk sac, as development proceeded (FIG. **3**). Against expectations, expression of YS68 was low in the AGM region at E10.5, when definitive hematopoiesis begins (FIG. **5**A). On the other hand, in liver, thymus, and spleen known to function as sites for hematopoiesis in the embryonic stage, expression of YS68 was very high (FIG. **4**) and correlated to the period when these tissues function as hematopoietic organs.

Furthermore, the expression distribution of YS68 in mouse embryo was analyzed by in situ hybridization. A vector constructed by inserting a 545 by cDNA of the 5'-region of YS68 (positions 898 to 1443) into pBluescript II was used as a template to perform in vitro transcription using T7 RNA polymerase or T3 RNA polymerase (Boeringer Mannheim), and to synthesize sense or antisense ^{35}S-labeled RNA, respectively. The mouse embryo was removed and frozen to produce slices using a cryostat. After immobilization and acetylation with 4% paraformaldehyde/PBT, hybridization was performed overnight at 55° C. with the above-mentioned RNA probe. After treating the reaction solution with RNase A, it was washed several times and autoradiography was performed.

The expression of YS68 was the strongest in liver at E11.5 (FIG. **6**). YS68 was mainly strongly expressed in liver and in the developing thymus, and expression was also confirmed in lungs and neural tube at E14.5 (FIG. **7**).

These results indicate that the expression of YS68 is localized in tissues where active hematopoiesis takes place in a period-specific manner, and strongly suggests that YS68 is a molecule involved in primitive hematopoiesis. Its expression was low in the E10.5 AGM region, which is thought to be the site of development for hematopoietic cells. However this may be due to the absolute number of cells involved in hematopoiesis within the entire AGM region, which is not so high. In fact, Suda et al. revealed that the percentage of hemangioblasts in the AGM region at E10.5 is 5% or less using TEK as a marker for hemangioblasts (Hamaguchi et al., Blood 93:1549-1556, 1999). On the other hand, when E10.5 AGM region is dispersed and cultivated on a dish, the emergence of hematocytes can be confirmed around the 5th day of cultivation (Mukouyama et al., Immunity 8:105-114, 1998). Interestingly, the expression of YS68 had increased in AGM derived cells cultivated for 5 days (FIG. **4**B). According to these results, the expression of YS68 is expected to rise in cells that have acquired hematopoietic ability, or in immature hematocytes.

Example 3

Full-Length Cloning of Mouse and Human YS68

Using primers constructed from the YS68 gene sequence obtained so far, 5'-RACE was performed using the mouse 15-day Embryo Marathon-Ready cDNA and human fetal liver Marathon-Ready cDNA (Clonetech) as templates, to clone the upstream 5' region of mouse and human YS68 gene. Full-length human and mouse cDNA sequences were determined by repeating this 5'-RACE protocol.

Consequently, human and mouse YS68 (SEQ ID NOs: 14 and 12, respectively) were anticipated to encode 2,266 and 2,243 amino acids, respectively (FIG. **9**). Comparing the human (SEQ ID NO: 14) and mouse (SEQ ID NO: 12) amino acid sequences, interestingly, the N-terminal region (human 1-1137 of SEQ ID NO: 14, mouse 1-1137 of SEQ ID NO: 12) had a very high homology of 87%, whereas the homology in the central region (human 1138-1683 of SEQ ID NO: 14, mouse 1138-1679 of SEQ ID NO: 12) was 57%, and that in the C-terminal region (human 1684-2266 of SEQ ID NO: 14, mouse 1680-2243 of SEQ ID NO: 12) was very low, showing a homology of 45%. In the C-terminal region with low homology, many nuclear transport signals existed. On the other hand, in the N-terminal region with high homology, two WD repeats existed, which repeats are known to be necessary for interaction among proteins. Since the homology in this region is very high between humans and mice, this region is anticipated to be important for the function of YS68.

Example 4

Proteins Binding to YS68

It was expected that YS68 is bound to some protein in vivo because a protein-binding site (WD repeats) exists in the N-terminal region of YS68. Therefore, cell lysate was prepared from cultivated cells of embryonic liver and immunoprecipitation with anti-YS68 antibody was performed. Then, SDS polyacrylamide gel electrophoresis was performed to investigate whether a protein that coprecipitates with YS68 exists. Specifically, cultivated mouse liver cells at E14.5 were solubilized with lysis buffer (0.5% NP-40, 10 mM Tris-HCl pH7.6, 150 mM NaCl, 5 mM EDTA, 2 mM Na_3VO_4, 1 mM phenylmethylsulfonyl fluoride, and 5 μg/ml aprotinin). After incubation overnight at 4° C. with anti-YS68 antibodies, pro-

tein G was added and was further incubated for 1 hour. SDS polyacrylamide gel electrophoresis was conducted after immunoprecipitation, and the gel was stained with silver.

Consequently, existence of multiple molecules that coprecipitate with YS68 within cells of embryonic liver was confirmed (FIG. **10**). This suggested that YS68 functions by binding to several types of proteins within the cell.

Example 5

Expression Site of YS68 within Tissues

For detailed analysis of the YS68 expression site, the YS68 protein was used to immunize rabbits to produce polyclonal antibodies against YS68. The protein encoding the 1208-1482 amino acid region of mouse YS68 was expressed in *E. coli*, was purified according to standard procedures, and was used as the antigen in the production of YS68 polyclonal antibodies. Immunization was carried out on rabbits (New Zealand White, 2.5 kg, female) using 200 μg antigen for 1 immunization, with an interval of 10 days for 4 immunizations. Then upon collection of whole blood, antiserum was obtained. Furthermore, an affinity column with immobilized antigens was prepared, and anti-YS68 polyclonal antibodies were purified from the antiserum.

Using these antibodies, the expression site in the AGM region of E11.5 embryo was investigated by immunostaining. Immunostaining was conducted as follows. First, slices of frozen mouse embryo were prepared using a cryostat (Leica). This was immobilized with 4% formaldehyde and was treated with methanol. After treatment with 0.3% aqueous hydrogen peroxide, blocking was carried out with 3% BSA, then upon reaction with primary antibodies overnight at 4° C. and with secondary antibodies (HRP-labeled anti-rabbit IgG) at room temperature for 1 hour, washing was repeated 3 times with PBS, and visualization was accomplished by the addition of substrate (Metal Enhanced DAB substrate kit, Pierce).

Consequently, the hematocytes existing in the endothelium were stained using red blood cell marker TER119 (used as a control; FIG. **11**A, B), whereas, the vascular endothelium was stained specifically using anti-YS68 antibody (FIGS. **11**C, D, and E). Interestingly, YS68 was darkly stained in the hematocytes emerging from the endothelium cells (FIG. **11**E, arrow). In addition, strong expression of YS68 was indicated in the vascular endothelium of the umbilical vein (FIG. **11**F). In contrast to TER119, which selectively stained hematocytes in the blood vessel, YS68 expression was stronger in vascular endothelium than in hematocytes in E9.5 yolk sacs (FIGS. **11**G and H).

Example 6

Expression of YS68 within Cells

A liver was surgically removed from an embryo (E14.5), cut into small pieces with tweezers, and incubated in cell dissociation buffer (Gibco) at 37° C. for 30 minutes. The cells were further treated with 0.1% collagenase at 37° C. for 1 hour, and were loosened by pipetting. After washing several times with PBS, the cells were suspended in DMEM containing 10% FCS, and were cultivated on a 10-cm dish.

To investigate the localization of endogenous YS68 within cells, cultured hepatic cells were stained with anti-YS68 antibodies. First, the cells were fixed with 4% formalin, and then treated with 0.1% Triton-X 100 for cell staining. Next, cells were reacted with the primary antibodies, and then with secondary antibodies. The cells were visualized in the same manner as in Example 5.

Consequently, although YS68 has multiple nuclear transport signals, strong expression was found not only in the nucleus, but also around the nucleus, which expression depended on cells (FIG. **12**). Next, similar analysis for the expression in hematocytes was carried out. YS68 expression in hematocytes separated from embryonic liver was found to have varied strengths of expression depending on the cell type (FIG. **13**B).

Therefore, the group of hematocytes was sorted using CD34, which is a marker for immature hematocytes, and YS68 expression in CD34-positive cells was investigated. To collect CD34-positive cells, embryonic liver (E14.5) was incubated in a dissociation buffer at 37° C. for 30 minutes, and then the cells were dissociated by pipetting in PBS. After passing through a nylon mesh filter (Falcon), the cells were suspended in a sample buffer (0.5% BSA, 2 mM EDTA in PBS). The cells were reacted with biotin labeled anti-CD34 antibodies (Pharmingen), followed by FITC labeled streptavidin at 4° C., and then were incubated with anti-FITC microbeads. CD34 positive cells were eluted using MACS (Magnetic Cell Sorting) column according to the instructed protocol. The cells were centrifuged on a slide glass at 400 rpm for 5 minutes to fix them onto the slide glass. Cell staining was performed in the same manner as described above.

Consequently, hematocytes that were concentrated using anti-CD34 antibodies (FIG. **12**D) showed a higher expression of YS68 compared to hematocytes that passed through the CD34 column (FIG. **12**C). Therefore, YS68 expression is anticipated in less differentiated CD34 positive hematocytes.

Example 7

Localization of Each Domain of YS68 within Cells

Using cDNA prepared from mouse embryonic liver as a template, cDNA encoding the N-terminal region (amino acids 5-1148) and C-terminal region (amino acids 981-2243) of mouse YS68 (SEQ ID NO: 12) were amplified by PCR. The amplified cDNAs were inserted downstream of the Flag region of animal cell expression vector pEFBOSE-F to produce pEFBOSE-F-YS68(5-1148) and pEFBOSE-F-YS68 (981-2243) that expresses the N-terminal region of YS68 and the C-terminal region of YS68 (SEQ ID NO: 12), respectively. The expression vectors were then transfected into COS-7 cells using lipofectamine 2000 (Gibco), and 24 hours later, the cells were immobilized with methanol. To investigate the localizations of each YS68 expressed within the cells, the cells were reacted with anti-Flag antibody, followed by peroxidase-labeled anti-mouse IgG, and finally substrate was added for visualization.

Due to the multiple nuclear transport signals in the YS68 C-terminal region (FIG. **9**), localization of YS68 in the nucleus was anticipated; however, endogenous YS68 was localized not only in the nucleus but also around the nucleus (FIG. **12**). Additionally, constructs lacking the YS68 N-terminal region or the C-terminal region were prepared and were expressed in COS cells, and their localizations were investigated. The results confirmed that YS68 lacking the C-terminal region had strong tendency to localize in the cytoplasm, and YS68 lacking the N-terminal region in the nucleus (FIG. **14**). These results suggested the possibility that the N-terminal region is inhibiting the transfer of YS68 into the nucleus. Since two WD repeats necessary for protein interaction exist

in the N-terminal region, it was speculated that binding of this region to some molecule might possibly inhibit the transfer into the nucleus.

INDUSTRIAL APPLICABILITY

The present invention provides novel "YS68" proteins predicted to be involved in primitive hematopoiesis and genes encoding the proteins. The genes may be utilized as markers for hematopoietic cells involved in primitive hematopoiesis and as factors regulating hematopoiesis. In addition, they may be utilized for purification and cloning of new factors involved in hematopoiesis, and even as tools for drug development for various diseases arising due to abnormalities in expression of the genes of this invention caused by abnormalities in expression regulation in vivo. Further, the "YS68" genes of this invention may be involved in blood tumors. Therefore, drug development against tumors utilizing the proteins of this invention is anticipated. By designing medicaments that target the genes of this invention, development of drugs that have new mechanisms of action may be enabled. Proteins and genes derived from humans are especially preferred in drug development compared to those derived from other organisms

SEQUENCE LISTING

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        275                 280                 285

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    290                 295                 300

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Lys Thr Ser Asp Lys Asn Thr Tyr Phe Pro Leu Asp Val Pro Ala Lys
305                 310                 315                 320

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Gly Pro Gln Lys Val Val Ala Glu Ser Leu Ala Thr His Ser Gly Arg
                325                 330                 335

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    770                 775                 780

gtt gcc act cct aag aag aga act aga aaa att aaa gaa act cct gag     2401
Val Ala Thr Pro Lys Lys Arg Thr Arg Lys Ile Lys Glu Thr Pro Glu
785                 790                 795                 800

tct tct gaa agg acc tgt tct gac cta aaa gta gca cct gag aac caa     2449
Ser Ser Glu Arg Thr Cys Ser Asp Leu Lys Val Ala Pro Glu Asn Gln
                805                 810                 815

ctg aca gct cag aat cct ccc gct cct agg aga aga aag aag aag gac     2497
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Leu Thr Ala Gln Asn Pro Pro Ala Pro Arg Arg Arg Lys Lys Lys Asp
            820                 825                 830

gtt agc caa ggc aca ctg cca agt tct ggt gct gtg gag ccg gag ccg     2545
Val Ser Gln Gly Thr Leu Pro Ser Ser Gly Ala Val Glu Pro Glu Pro
        835                 840                 845

gaa cct cag ggt acg ccg gga aga ctg agg ctg aga acg cag cca ccc     2593
Glu Pro Gln Gly Thr Pro Gly Arg Leu Arg Leu Arg Thr Gln Pro Pro
    850                 855                 860

gag cca gca gct gaa gaa act cct tct aga aca aaa gtc agg ctt tca     2641
Glu Pro Ala Ala Glu Glu Thr Pro Ser Arg Thr Lys Val Arg Leu Ser
865                 870                 875                 880

tct gtt aga aag gga acc cct aga aga ctt aag aag tct gta gaa aat     2689
Ser Val Arg Lys Gly Thr Pro Arg Arg Leu Lys Lys Ser Val Glu Asn
                885                 890                 895

ggg caa agt ata gaa att cta gat gat ctc aaa ggg agt gag gca gca     2737
Gly Gln Ser Ile Glu Ile Leu Asp Asp Leu Lys Gly Ser Glu Ala Ala
            900                 905                 910

agt cat gac ggg act gtc aca gag ctg agg aat gcc aat tta gaa gat     2785
Ser His Asp Gly Thr Val Thr Glu Leu Arg Asn Ala Asn Leu Glu Asp
        915                 920                 925

act cag aat atg gag tat aaa caa gat gaa cac agt gac cag caa ccg     2833
Thr Gln Asn Met Glu Tyr Lys Gln Asp Glu His Ser Asp Gln Gln Pro
    930                 935                 940

cct cta aaa cga aag agg gtc aga gag aga gaa gtt agt gtg tca agt     2881
Pro Leu Lys Arg Lys Arg Val Arg Glu Arg Glu Val Ser Val Ser Ser
945                 950                 955                 960

gtg aca gaa gag cca aag ctt gac tca tcc cag ttg cct ctt cag aca     2929
Val Thr Glu Glu Pro Lys Leu Asp Ser Ser Gln Leu Pro Leu Gln Thr
                965                 970                 975

gga ctc gat gta cct gcc acc cct agg aaa cgt ggt aga ccc agg aag     2977
Gly Leu Asp Val Pro Ala Thr Pro Arg Lys Arg Gly Arg Pro Arg Lys
            980                 985                 990

gta gtt ccc tta gaa gct gac ggt  ggc aca act ggt aag  gaa cag aca   3025
Val Val Pro Leu Glu Ala Asp Gly  Gly Thr Thr Gly Lys  Glu Gln Thr
        995                 1000                1005

agt cct  cag aag aaa gat gtt  ccg gtt gtc cgg aga  tct aca cgg      3070
Ser Pro  Gln Lys Lys Asp Val  Pro Val Val Arg Arg  Ser Thr Arg
    1010                1015                1020

aac acc  cca gct aga aat gtg  agt act tta naa aaa  tca gtt tta      3115
Asn Thr  Pro Ala Arg Asn Val  Ser Thr Leu Xaa Lys  Ser Val Leu
    1025                1030                1035

gtg cca  aat aag gaa gct gct  cta gtg gtg aca tct  aag agg aga      3160
Val Pro  Asn Lys Glu Ala Ala  Leu Val Val Thr Ser  Lys Arg Arg
    1040                1045                1050

cct aca  aag aag tct gca gag  gaa agc tca aaa gat  cca tca gcg      3205
Pro Thr  Lys Lys Ser Ala Glu  Glu Ser Ser Lys Asp  Pro Ser Ala
    1055                1060                1065

gca gtc  tca gac tgg gcg ggt  gga gca gcc cac aca  gag tcc gct      3250
Ala Val  Ser Asp Trp Ala Gly  Gly Ala Ala His Thr  Glu Ser Ala
    1070                1075                1080

gac cga  agg gac gga ctg ctt  gcc gcc gct gct ctc  acg cca tct      3295
Asp Arg  Arg Asp Gly Leu Leu  Ala Ala Ala Ala Leu  Thr Pro Ser
    1085                1090                1095

gcc cag  ggc aca agg act agg  tct aga agg acc atg  ttg ttg acg      3340
Ala Gln  Gly Thr Arg Thr Arg  Ser Arg Arg Thr Met  Leu Leu Thr
    1100                1105                1110

gac att  tct gaa ccc aaa act  gag cct tta ttt cct  cct cct tca      3385
Asp Ile  Ser Glu Pro Lys Thr  Glu Pro Leu Phe Pro  Pro Pro Ser
    1115                1120                1125

gtg aag  gtt cca aag aaa aaa  tca aaa gct gag aac  atg gag gcc      3430
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```
Val Lys  Val Pro Lys Lys Lys  Ser Lys Ala Glu Asn  Met Glu Ala
    1130                1135                1140

gca gcc  cag ctg aaa gaa ttg  gtg tca gat tta tct  tct cag ttt      3475
Ala Ala  Gln Leu Lys Glu Leu  Val Ser Asp Leu Ser  Ser Gln Phe
    1145                1150                1155

gtt gtt  tcc cct cct gcc ttg  aga acc agg cag aaa  agt ata tcc      3520
Val Val  Ser Pro Pro Ala Leu  Arg Thr Arg Gln Lys  Ser Ile Ser
    1160                1165                1170

aat act  tcc aag ctt cta ggt  gaa ctg gag agt gac  cct aaa cca      3565
Asn Thr  Ser Lys Leu Leu Gly  Glu Leu Glu Ser Asp  Pro Lys Pro
    1175                1180                1185

tta gag  atc ata gaa caa aaa  cca aaa aga agc agg  act gtg aag      3610
Leu Glu  Ile Ile Glu Gln Lys  Pro Lys Arg Ser Arg  Thr Val Lys
    1190                1195                1200

aca aga  gca agc aga aac aca  gga aaa gga agt tct  tgg tca cct      3655
Thr Arg  Ala Ser Arg Asn Thr  Gly Lys Gly Ser Ser  Trp Ser Pro
    1205                1210                1215

cct cct  gta gaa att aag ctg  gtt tct ccc ttg gcg  agt cca gtg      3700
Pro Pro  Val Glu Ile Lys Leu  Val Ser Pro Leu Ala  Ser Pro Val
    1220                1225                1230

gat gaa  ata aag acc ggc aag  cca aga aaa act gca  gaa ata gca      3745
Asp Glu  Ile Lys Thr Gly Lys  Pro Arg Lys Thr Ala  Glu Ile Ala
    1235                1240                1245

gga aaa  act ctt gga agg ggc  aga aag aag cca tct  tct ttt cca      3790
Gly Lys  Thr Leu Gly Arg Gly  Arg Lys Lys Pro Ser  Ser Phe Pro
    1250                1255                1260

aag caa  att tta cgc agg aaa  atg ctg taatttttag cccaagattt        3837
Lys Gln  Ile Leu Arg Arg Lys  Met Leu
    1265                1270

taacacgcac ctgtttgtaa aagtcaacag tatttgtgtg gattattaaa gtcaccaatt   3897

tggatgaaaa tactttatat aaattgtaca attttgtaag cagtaaatga gtaactccac   3957

atggagtgca gttcttgtag tgcaggcgtt ttatacgact tgatgcgttt atatcaatgt   4017

aaatatgact tatcattggg aggttaaata aactactgta aagtaaaaaa aaaaaaaaaa   4077

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa                           4115
```

<210> SEQ ID NO 2
<211> LENGTH: 1272
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1034)..(1034)
<223> OTHER INFORMATION: The 'Xaa' at location 1034 stands for Lys, Glu, or Gln.

<400> SEQUENCE: 2

```
Gln Ile Leu Lys Asn Asn Leu Met Ser Asp Arg Asp Pro Arg Leu Arg
1               5                  10                  15

Glu Arg Ser Val Thr Arg Asn Ser Ile Leu Asp Gln Tyr Gly Lys Ile
            20                  25                  30

Leu Pro Arg Val Gln Arg Lys Leu Ala Val Glu Arg Ala Lys Pro Tyr
        35                  40                  45

His Leu Ser Thr Ser Ser Val Phe His Glu Val Ser Arg Pro Lys Pro
    50                  55                  60

Leu Ser Ala Phe Pro Lys Lys Ala Ile Thr Gly Thr Val Leu Thr Arg
65                  70                  75                  80

Ser Thr Phe Ile Ser Asn Val Leu Ser Lys Ile Gly Glu Val Trp Ala
                85                  90                  95
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Ser His Glu Pro Arg Asn Gly Val Ser Leu Phe Asn Ser Pro Lys Thr
            100                 105                 110

Glu Gln Pro Ser Pro Val Val His Ser Phe Pro His Pro Glu Leu Pro
        115                 120                 125

Glu Ala Phe Val Gly Thr Pro Ile Ser Asn Thr Ser Gln Arg Ile Ser
    130                 135                 140

Arg Leu Leu Asp Leu Val Val His Pro Val Pro Gln Pro Ser Gln Cys
145                 150                 155                 160

Leu Glu Phe Ile Gln Gln Ser Pro Thr Arg Ser Pro Leu Cys Leu Leu
                165                 170                 175

Ser Ser Ser Leu Pro Leu Ser Ser Gln Phe Lys Arg Pro His Gln Asn
            180                 185                 190

Thr Ser Arg Pro Ser Glu Leu Leu Leu Leu Glu Thr Pro Leu Ile Val
        195                 200                 205

Lys Lys Ala Lys Ser Leu Ala Leu Ser Ala Thr Ser Ser Gly Phe Ala
    210                 215                 220

Glu Phe Thr Pro Pro Ser Ile Leu Arg Ser Gly Phe Arg Thr Thr Pro
225                 230                 235                 240

Leu Ala Ser Pro Ser Leu Ser Pro Gly Arg Ser Leu Thr Pro Pro Phe
                245                 250                 255

Arg Val Lys Glu Thr Arg Ile Ser Phe Met Glu Glu Gly Met Asn Thr
            260                 265                 270

His Trp Thr Asp Arg Ala Thr Asp Asp Arg Asn Thr Lys Ala Phe Val
        275                 280                 285

Ser Thr Ser Phe His Lys Cys Gly Leu Pro Ala Glu Thr Glu Trp Met
    290                 295                 300

Lys Thr Ser Asp Lys Asn Thr Tyr Phe Pro Leu Asp Val Pro Ala Lys
305                 310                 315                 320

Gly Pro Gln Lys Val Val Ala Glu Ser Leu Ala Thr His Ser Gly Arg
                325                 330                 335

Leu Glu Lys Leu Asp Val Ser Lys Glu Asp Ser Thr Ala Ser Thr Arg
            340                 345                 350

Ser Asp Gln Thr Ser Leu Glu Tyr His Asp Ala Pro Ser Pro Glu Asp
        355                 360                 365

Leu Glu Gly Ala Val Phe Val Ser Pro Lys Pro Ala Ser Ser Ser Thr
    370                 375                 380

Glu Leu Thr Thr Asn Ser Thr Leu Gln Thr Glu Arg Asp Asn Asp Lys
385                 390                 395                 400

Asp Ala Phe Lys Ser Glu Gly Thr Pro Ser Pro Val Lys Lys Gln Ile
                405                 410                 415

Gly Thr Gly Asp Ala Ala Val Glu Ala Phe Ser Glu Leu Ser Arg Leu
            420                 425                 430

Asp Pro Val Glu Arg Ala Glu Ala Ser Phe Gly Val Ser Ser Val Cys
        435                 440                 445

Glu Gly Glu Thr Ser Thr Ser Asn Ser Lys Thr Ser Val Leu Asp Gly
    450                 455                 460

Ile Val Pro Ile Glu Ser Arg Thr Ser Ile Leu Thr Ala Asp His Lys
465                 470                 475                 480

Glu Ser Val Ala Asn Thr Val Ala Asp Val Glu Ser Ser Gly Ser Thr
                485                 490                 495

Ser Ser Lys Cys Pro Val Thr Ser Glu Arg Ser Leu Gly Gln Lys Leu
            500                 505                 510

Thr Leu Asn Leu Lys Glu Asp Glu Ile Glu Ala His Val Pro Lys Glu
        515                 520                 525
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Asn Val Gly Leu Pro Glu Glu Ser Pro Arg Ile Ser Ala Ala Pro Ser
    530                 535                 540

Asp Thr His Glu Ile His Leu Ile Gly Cys Glu Asn Leu Glu Val Gln
545                 550                 555                 560

Asn Ser Glu Glu Glu Ala Lys Asn Leu Ser Phe Asp Glu Leu Tyr Pro
                565                 570                 575

Leu Gly Ala Glu Lys Leu Glu Tyr Asn Leu Ser Thr Ile Glu Gln Gln
            580                 585                 590

Phe Cys Asp Leu Pro Asp Asp Lys Asp Ser Ala Glu Cys Asp Ala Ala
        595                 600                 605

Glu Val Asp Gly Glu Leu Phe Val Ala Gln Ser Asn Phe Thr Leu Ile
    610                 615                 620

Leu Glu Gly Glu Glu Gly Glu Ala Glu Ala Ser Asp Ser Ala Ala Pro
625                 630                 635                 640

Asn Met Leu Pro Lys Ser Thr Lys Glu Lys Pro Val Cys Tyr Arg Glu
                645                 650                 655

Pro His Asn Gln Glu Arg Val Thr Asp Leu Pro Ser Ala Val Thr Ala
            660                 665                 670

Asp Gln Glu Ser His Lys Val Glu Thr Leu Pro Tyr Val Pro Glu Pro
        675                 680                 685

Val Lys Val Ala Ile Ala Glu Asn Leu Leu Asp Val Ile Lys Asp Thr
    690                 695                 700

Arg Ser Lys Glu Ala Thr Pro Val Ala Ala Gly Glu Ala Gly Asp Glu
705                 710                 715                 720

Asp Gly Ala Val Ile Val Ser Lys Ala Ala His Ser Ser Arg Leu Thr
                725                 730                 735

Asn Ser Thr Pro Lys Thr Val Lys Glu Pro Arg Ala Glu Thr Val Asn
            740                 745                 750

Thr Ser Gln Ser Asp Asp Met Val Ser Ser Arg Thr Leu Thr Arg Arg
        755                 760                 765

Gln His Ala Leu Ser Leu Asn Val Thr Ser Glu Gln Glu Pro Ser Ala
    770                 775                 780

Val Ala Thr Pro Lys Lys Arg Thr Arg Lys Ile Lys Glu Thr Pro Glu
785                 790                 795                 800

Ser Ser Glu Arg Thr Cys Ser Asp Leu Lys Val Ala Pro Glu Asn Gln
                805                 810                 815

Leu Thr Ala Gln Asn Pro Pro Ala Pro Arg Arg Arg Lys Lys Lys Asp
            820                 825                 830

Val Ser Gln Gly Thr Leu Pro Ser Ser Gly Ala Val Glu Pro Glu Pro
        835                 840                 845

Glu Pro Gln Gly Thr Pro Gly Arg Leu Arg Leu Arg Thr Gln Pro Pro
    850                 855                 860

Glu Pro Ala Ala Glu Glu Thr Pro Ser Arg Thr Lys Val Arg Leu Ser
865                 870                 875                 880

Ser Val Arg Lys Gly Thr Pro Arg Arg Leu Lys Lys Ser Val Glu Asn
                885                 890                 895

Gly Gln Ser Ile Glu Ile Leu Asp Asp Leu Lys Gly Ser Glu Ala Ala
            900                 905                 910

Ser His Asp Gly Thr Val Thr Glu Leu Arg Asn Ala Asn Leu Glu Asp
        915                 920                 925

Thr Gln Asn Met Glu Tyr Lys Gln Asp Glu His Ser Asp Gln Gln Pro
    930                 935                 940

Pro Leu Lys Arg Lys Arg Val Arg Glu Arg Glu Val Ser Val Ser Ser
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945                 950                 955                 960

Val Thr Glu Glu Pro Lys Leu Asp Ser Ser Gln Leu Pro Leu Gln Thr
                965                 970                 975

Gly Leu Asp Val Pro Ala Thr Pro Arg Lys Arg Gly Arg Pro Arg Lys
            980                 985                 990

Val Val Pro Leu Glu Ala Asp Gly  Gly Thr Thr Gly Lys  Glu Gln Thr
        995                1000                1005

Ser Pro  Gln Lys Lys Asp Val  Pro Val Val Arg Arg  Ser Thr Arg
    1010                1015                1020

Asn Thr  Pro Ala Arg Asn Val  Ser Thr Leu Xaa Lys  Ser Val Leu
    1025                1030                1035

Val Pro  Asn Lys Glu Ala Ala  Leu Val Val Thr Ser  Lys Arg Arg
    1040                1045                1050

Pro Thr  Lys Lys Ser Ala Glu  Glu Ser Ser Lys Asp  Pro Ser Ala
    1055                1060                1065

Ala Val  Ser Asp Trp Ala Gly  Gly Ala Ala His Thr  Glu Ser Ala
    1070                1075                1080

Asp Arg  Arg Asp Gly Leu Leu  Ala Ala Ala Ala Leu  Thr Pro Ser
    1085                1090                1095

Ala Gln  Gly Thr Arg Thr Arg  Ser Arg Arg Thr Met  Leu Leu Thr
    1100                1105                1110

Asp Ile  Ser Glu Pro Lys Thr  Glu Pro Leu Phe Pro  Pro Pro Ser
    1115                1120                1125

Val Lys  Val Pro Lys Lys Lys  Ser Lys Ala Glu Asn  Met Glu Ala
    1130                1135                1140

Ala Ala  Gln Leu Lys Glu Leu  Val Ser Asp Leu Ser  Ser Gln Phe
    1145                1150                1155

Val Val  Ser Pro Pro Ala Leu  Arg Thr Arg Gln Lys  Ser Ile Ser
    1160                1165                1170

Asn Thr  Ser Lys Leu Leu Gly  Glu Leu Glu Ser Asp  Pro Lys Pro
    1175                1180                1185

Leu Glu  Ile Ile Glu Gln Lys  Pro Lys Arg Ser Arg  Thr Val Lys
    1190                1195                1200

Thr Arg  Ala Ser Arg Asn Thr  Gly Lys Gly Ser Ser  Trp Ser Pro
    1205                1210                1215

Pro Pro  Val Glu Ile Lys Leu  Val Ser Pro Leu Ala  Ser Pro Val
    1220                1225                1230

Asp Glu  Ile Lys Thr Gly Lys  Pro Arg Lys Thr Ala  Glu Ile Ala
    1235                1240                1245

Gly Lys  Thr Leu Gly Arg Gly  Arg Lys Lys Pro Ser  Ser Phe Pro
    1250                1255                1260

Lys Gln  Ile Leu Arg Arg Lys  Met Leu
    1265                1270


<210> SEQ ID NO 3
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Primer Sequence

<400> SEQUENCE: 3

cacccgtgaa gaaacaaata ggca                                          24


<210> SEQ ID NO 4
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<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially Synthesized Primer Sequence

<400> SEQUENCE: 4

cctttggtac atgagcttct attt 24

<210> SEQ ID NO 5
<211> LENGTH: 4883
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(4590)

<400> SEQUENCE: 5

```
gag aag ttg tgg aaa cga gat gaa gga ggc aca gga aaa tat cct cct       48
Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Lys Tyr Pro Pro
1               5                   10                  15

gct agt ctg cat gca gta ctt gat atg tac cta tta gac ggc gtt act       96
Ala Ser Leu His Ala Val Leu Asp Met Tyr Leu Leu Asp Gly Val Thr
            20                  25                  30

gaa gca gcc aaa cac tct att acc att tat ttg cta ctt gat att atg      144
Glu Ala Ala Lys His Ser Ile Thr Ile Tyr Leu Leu Leu Asp Ile Met
        35                  40                  45

tat tcc ttt ccc aac aaa aca gac act ccc att gaa tct ttc cca act      192
Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe Pro Thr
    50                  55                  60

gta ttt gcc att tct tgg ggc caa gtt aaa ctt att cag ggg ttt tgg      240
Val Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Ile Gln Gly Phe Trp
65                  70                  75                  80

ttg ata gat cat aat gac tat gag agt ggt ttg gat ctt ttg ttt cat      288
Leu Ile Asp His Asn Asp Tyr Glu Ser Gly Leu Asp Leu Leu Phe His
                85                  90                  95

cca gct act gca aaa cct ttg tca tgg caa cat tca aag att att cag      336
Pro Ala Thr Ala Lys Pro Leu Ser Trp Gln His Ser Lys Ile Ile Gln
            100                 105                 110

gca ttc atg agt cag ggc gag cac aga caa gcc ctc aga tat att cag      384
Ala Phe Met Ser Gln Gly Glu His Arg Gln Ala Leu Arg Tyr Ile Gln
        115                 120                 125

aca atg aag cca aca gtg tcc agt ggt aac gat gtt atc ctt cac ctc      432
Thr Met Lys Pro Thr Val Ser Ser Gly Asn Asp Val Ile Leu His Leu
    130                 135                 140

act gtt ttg ctt ttt aat agg tgt atg gtt gaa gcc tgg aat ttt ttg      480
Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn Phe Leu
145                 150                 155                 160

cgg caa cat tgc aat agg ttg aat ata gag gag tta ctg aag cac atg      528
Arg Gln His Cys Asn Arg Leu Asn Ile Glu Glu Leu Leu Lys His Met
                165                 170                 175

tat gaa gtc tgt cag gaa atg ggc ttg atg gaa gat tta ctg aag tta      576
Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu Lys Leu
            180                 185                 190

cca ttt aca gac act gag cag gaa tgt tta gtg aaa ttt ttg cag tcc      624
Pro Phe Thr Asp Thr Glu Gln Glu Cys Leu Val Lys Phe Leu Gln Ser
        195                 200                 205

agt gcc agc gtt cag aat cat gaa ttc ctt tta gtg cac cat ttg cag      672
Ser Ala Ser Val Gln Asn His Glu Phe Leu Leu Val His His Leu Gln
    210                 215                 220

cgt gcc aat tat gtg cct gcc ttg aag ctg aac caa act ctg aag att      720
Arg Ala Asn Tyr Val Pro Ala Leu Lys Leu Asn Gln Thr Leu Lys Ile
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225                 230                 235                 240

aat gtt atg aat gat cgt gat cct cgt ttg cgg gag aga tca ctg gct      768
Asn Val Met Asn Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser Leu Ala
                245                 250                 255

cga aat tct ata tta gac cag tat gga aaa atc ctt cct aga gtc cat      816
Arg Asn Ser Ile Leu Asp Gln Tyr Gly Lys Ile Leu Pro Arg Val His
            260                 265                 270

cga aaa tta gcc att gaa cga gct aag cct tat cat ctg tca aca tca      864
Arg Lys Leu Ala Ile Glu Arg Ala Lys Pro Tyr His Leu Ser Thr Ser
        275                 280                 285

tca gtt ttt cga tta gtt tct aga ccc aaa cca tta tca gca gtt cca      912
Ser Val Phe Arg Leu Val Ser Arg Pro Lys Pro Leu Ser Ala Val Pro
    290                 295                 300

aag caa gtt gta aca gga act gtg ttg aca aga tct gtt ttc atc aac      960
Lys Gln Val Val Thr Gly Thr Val Leu Thr Arg Ser Val Phe Ile Asn
305                 310                 315                 320

aat gtg tta tct aaa att gga gaa gtt tgg gca agc aaa gaa cct ata     1008
Asn Val Leu Ser Lys Ile Gly Glu Val Trp Ala Ser Lys Glu Pro Ile
                325                 330                 335

aat agc acc aca cct ttc aat agt tct aaa ata gaa gaa cca tct cct     1056
Asn Ser Thr Thr Pro Phe Asn Ser Ser Lys Ile Glu Glu Pro Ser Pro
            340                 345                 350

ata gtg tat tcg ctc cca gct cca gag ctg cct gag gca ttt ttt gga     1104
Ile Val Tyr Ser Leu Pro Ala Pro Glu Leu Pro Glu Ala Phe Phe Gly
        355                 360                 365

aca cca att tca aaa gca tca caa aaa att tct aga ctg cta gat ttg     1152
Thr Pro Ile Ser Lys Ala Ser Gln Lys Ile Ser Arg Leu Leu Asp Leu
    370                 375                 380

gtt gtt cag cct gtc ccc cgg cct tct cag tgt tcg gag ttt att cag     1200
Val Val Gln Pro Val Pro Arg Pro Ser Gln Cys Ser Glu Phe Ile Gln
385                 390                 395                 400

caa agc tcc atg aaa tct cct ttg tac cta gta tcc cgt tca ctg ccc     1248
Gln Ser Ser Met Lys Ser Pro Leu Tyr Leu Val Ser Arg Ser Leu Pro
                405                 410                 415

tca agt tcg caa tta aaa gga tcg cct cag gcc atc tcc agg gct tca     1296
Ser Ser Ser Gln Leu Lys Gly Ser Pro Gln Ala Ile Ser Arg Ala Ser
            420                 425                 430

gaa tta cat ttg ctt gaa act cct ctt gta gtt aag aaa gct aaa agt     1344
Glu Leu His Leu Leu Glu Thr Pro Leu Val Val Lys Lys Ala Lys Ser
        435                 440                 445

ttg gcc atg tca gtt act act tct gga ttt tct gag ttc act cct cag     1392
Leu Ala Met Ser Val Thr Thr Ser Gly Phe Ser Glu Phe Thr Pro Gln
    450                 455                 460

tcc atc ctg agg tct act cct cga tca aca cct tta gca tct ccc tct     1440
Ser Ile Leu Arg Ser Thr Pro Arg Ser Thr Pro Leu Ala Ser Pro Ser
465                 470                 475                 480

cca tca cct gga agg tct cct caa cga ctt aaa gaa act aga att tca     1488
Pro Ser Pro Gly Arg Ser Pro Gln Arg Leu Lys Glu Thr Arg Ile Ser
                485                 490                 495

ttt gtg gaa gaa gat gtc cac cca aaa tgg att cct ggg gct gca gat     1536
Phe Val Glu Glu Asp Val His Pro Lys Trp Ile Pro Gly Ala Ala Asp
            500                 505                 510

gat agc aaa tta gaa gta ttt act aca cct aaa aaa tgt gca gtt cca     1584
Asp Ser Lys Leu Glu Val Phe Thr Thr Pro Lys Lys Cys Ala Val Pro
        515                 520                 525

gtg gaa act gaa tgg ccg aag agc aaa gat agg acc aca tct ttt ttc     1632
Val Glu Thr Glu Trp Pro Lys Ser Lys Asp Arg Thr Thr Ser Phe Phe
    530                 535                 540

ctg aac agc cct gaa aag gag cat caa gaa atg gat gag ggg tca caa     1680
Leu Asn Ser Pro Glu Lys Glu His Gln Glu Met Asp Glu Gly Ser Gln
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545                 550                 555                 560

agt tta gag aaa ctg gat gtg agc aaa gga aac agc agt gtt tca atc     1728
Ser Leu Glu Lys Leu Asp Val Ser Lys Gly Asn Ser Ser Val Ser Ile
                565                 570                 575

aca tcc gat gag act acc tta gag tat cag gat gca ccg tca ccg gaa     1776
Thr Ser Asp Glu Thr Thr Leu Glu Tyr Gln Asp Ala Pro Ser Pro Glu
            580                 585                 590

gac ctt gaa gag act gtt ttc acg gcc tct aag ccc aaa agc tct tcc     1824
Asp Leu Glu Glu Thr Val Phe Thr Ala Ser Lys Pro Lys Ser Ser Ser
        595                 600                 605

act gca cta act act aat gta act gaa caa act gaa aag gat gga gat     1872
Thr Ala Leu Thr Thr Asn Val Thr Glu Gln Thr Glu Lys Asp Gly Asp
    610                 615                 620

aaa gat gta ttt gca tca gaa gta act cct tca gac cta cag aaa caa     1920
Lys Asp Val Phe Ala Ser Glu Val Thr Pro Ser Asp Leu Gln Lys Gln
625                 630                 635                 640

atg ggc aat tta gaa gat gca gaa aca aag gat ctc tta gtt gca gca     1968
Met Gly Asn Leu Glu Asp Ala Glu Thr Lys Asp Leu Leu Val Ala Ala
                645                 650                 655

gag gca ttt tca gaa ttg aat cac tta agc ccg gtt caa gga act gaa     2016
Glu Ala Phe Ser Glu Leu Asn His Leu Ser Pro Val Gln Gly Thr Glu
            660                 665                 670

gct tct ctt tgt gca cca tca gtc tat gaa ggg aaa atc ttc acc cag     2064
Ala Ser Leu Cys Ala Pro Ser Val Tyr Glu Gly Lys Ile Phe Thr Gln
        675                 680                 685

aag tcc aag gta cca gtg ttg gac gaa gga tta aca tct gtt gaa acc     2112
Lys Ser Lys Val Pro Val Leu Asp Glu Gly Leu Thr Ser Val Glu Thr
    690                 695                 700

tac acc cct gca att aga gca aat gac aat aaa tct atg gct gat gtc     2160
Tyr Thr Pro Ala Ile Arg Ala Asn Asp Asn Lys Ser Met Ala Asp Val
705                 710                 715                 720

ctt ggt gat ggt gga aac tcc tcg ctc act atc tct gaa ggt cct att     2208
Leu Gly Asp Gly Gly Asn Ser Ser Leu Thr Ile Ser Glu Gly Pro Ile
                725                 730                 735

gtc tct gag cgc agg ctt aac cag gaa gta gcg ctg aac tta aaa gaa     2256
Val Ser Glu Arg Arg Leu Asn Gln Glu Val Ala Leu Asn Leu Lys Glu
            740                 745                 750

gat cat gaa gta gaa gtt ggt gta cta aaa gaa agt gtt gac tta cca     2304
Asp His Glu Val Glu Val Gly Val Leu Lys Glu Ser Val Asp Leu Pro
        755                 760                 765

gaa gaa aag ctt cca att tct gac agc cct cct gat act caa gaa att     2352
Glu Glu Lys Leu Pro Ile Ser Asp Ser Pro Pro Asp Thr Gln Glu Ile
    770                 775                 780

cat gtg att gaa caa gaa aag ctt gaa gct caa gat tca gga gaa gag     2400
His Val Ile Glu Gln Glu Lys Leu Glu Ala Gln Asp Ser Gly Glu Glu
785                 790                 795                 800

gct agg aat ctt tca ttt aat gag tta tat ccc tct gga aca ctt aag     2448
Ala Arg Asn Leu Ser Phe Asn Glu Leu Tyr Pro Ser Gly Thr Leu Lys
                805                 810                 815

ctt cag tac aat ttt gat act att gac caa cag ttt tgt gac tta gct     2496
Leu Gln Tyr Asn Phe Asp Thr Ile Asp Gln Gln Phe Cys Asp Leu Ala
            820                 825                 830

gat aac aaa gac act gct gaa tgt gac att gct gaa gta gat ggg gaa     2544
Asp Asn Lys Asp Thr Ala Glu Cys Asp Ile Ala Glu Val Asp Gly Glu
        835                 840                 845

ctt ttt gtg gct caa agc aac ttt acc ttg ata ttg gaa ggt gaa gaa     2592
Leu Phe Val Ala Gln Ser Asn Phe Thr Leu Ile Leu Glu Gly Glu Glu
    850                 855                 860

gga gaa gtt gag cca ggt gat ttt gca tca tct gat gtg tta cct aaa     2640
Gly Glu Val Glu Pro Gly Asp Phe Ala Ser Ser Asp Val Leu Pro Lys
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865                 870                 875                 880

gca gct aac aca gca act gaa gaa aaa ctt gta tgc agt ggg gaa aat     2688
Ala Ala Asn Thr Ala Thr Glu Glu Lys Leu Val Cys Ser Gly Glu Asn
                885                 890                 895

gat aat cat gga caa att gca aat ttg cca tct gcc gta act agt gac     2736
Asp Asn His Gly Gln Ile Ala Asn Leu Pro Ser Ala Val Thr Ser Asp
            900                 905                 910

caa aag tcc caa aaa gta gac act tta cca tat gtg cct gaa cct att     2784
Gln Lys Ser Gln Lys Val Asp Thr Leu Pro Tyr Val Pro Glu Pro Ile
        915                 920                 925

aaa gta gca att gca gaa aat tta cta gat gta att aaa gac aca aga     2832
Lys Val Ala Ile Ala Glu Asn Leu Leu Asp Val Ile Lys Asp Thr Arg
    930                 935                 940

agt aaa gaa att act tca gat aca atg gaa cag tcc att cat gaa aca     2880
Ser Lys Glu Ile Thr Ser Asp Thr Met Glu Gln Ser Ile His Glu Thr
945                 950                 955                 960

ata cct tta gtg agc caa aac ata atg tgt ccc act aaa ttg gtc aaa     2928
Ile Pro Leu Val Ser Gln Asn Ile Met Cys Pro Thr Lys Leu Val Lys
                965                 970                 975

tct gca ttt aag act gct cag gaa aca agc aca atg act atg aat gtc     2976
Ser Ala Phe Lys Thr Ala Gln Glu Thr Ser Thr Met Thr Met Asn Val
            980                 985                 990

agc cag gtt gat gac gtg gtt tcc  tcc aaa act cgt acg  aga ggt caa   3024
Ser Gln Val Asp Asp Val Val Ser  Ser Lys Thr Arg Thr  Arg Gly Gln
        995                 1000                1005

cgt atc  caa aac gtg aat gtc  aaa tca gca caa cag  gaa gca tca      3069
Arg Ile  Gln Asn Val Asn Val  Lys Ser Ala Gln Gln  Glu Ala Ser
    1010                1015                1020

gca gat  gtt gct act cct aag  atg cca ggg cag tca  gtc agg aag      3114
Ala Asp  Val Ala Thr Pro Lys  Met Pro Gly Gln Ser  Val Arg Lys
    1025                1030                1035

aaa act  agg aag gca aaa gaa  att tct gaa gct tct  gaa aac atc      3159
Lys Thr  Arg Lys Ala Lys Glu  Ile Ser Glu Ala Ser  Glu Asn Ile
    1040                1045                1050

tat tct  gat gtc aga gga cta  ttt cag aac cag caa  ata cct caa      3204
Tyr Ser  Asp Val Arg Gly Leu  Phe Gln Asn Gln Gln  Ile Pro Gln
    1055                1060                1065

aat tct  gtt acg cct agg aga  gga agg aga aag aaa  gaa gtt aat      3249
Asn Ser  Val Thr Pro Arg Arg  Gly Arg Arg Lys Lys  Glu Val Asn
    1070                1075                1080

cag gac  ata cta gaa aac acc  agt tct gtg gaa caa  gaa tta cag      3294
Gln Asp  Ile Leu Glu Asn Thr  Ser Ser Val Glu Gln  Glu Leu Gln
    1085                1090                1095

atc act  aca ggt agg gaa tca  aaa aga tta aaa tca  tct cag ctg      3339
Ile Thr  Thr Gly Arg Glu Ser  Lys Arg Leu Lys Ser  Ser Gln Leu
    1100                1105                1110

ttg gaa  cca gca gtt gaa gaa  act act aaa aaa gaa  gtt aag gtt      3384
Leu Glu  Pro Ala Val Glu Glu  Thr Thr Lys Lys Glu  Val Lys Val
    1115                1120                1125

tca tct  gtt aca aaa agg act  cct aga aga att aaa  aga tct gta      3429
Ser Ser  Val Thr Lys Arg Thr  Pro Arg Arg Ile Lys  Arg Ser Val
    1130                1135                1140

gaa aat  cag gaa agt gtt gaa  att ata aat gat cta  aaa gtt agt      3474
Glu Asn  Gln Glu Ser Val Glu  Ile Ile Asn Asp Leu  Lys Val Ser
    1145                1150                1155

acg gta  aca agt cct agc aga  atg atc aga aaa ttg  aga agt act      3519
Thr Val  Thr Ser Pro Ser Arg  Met Ile Arg Lys Leu  Arg Ser Thr
    1160                1165                1170

aat tta  gat gct tct gaa aat  aca gga aat aag caa  gat gat aaa      3564
Asn Leu  Asp Ala Ser Glu Asn  Thr Gly Asn Lys Gln  Asp Asp Lys
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    1175                1180                1185

tcc agt  gac aag cag ctg cgt  att aaa cat gtt aga  agg gtc aga      3609
Ser Ser  Asp Lys Gln Leu Arg  Ile Lys His Val Arg  Arg Val Arg
    1190                1195                1200

ggg aga  gaa gtt agt cca tca  gat gtg aga gaa gac  tcc aac ctt      3654
Gly Arg  Glu Val Ser Pro Ser  Asp Val Arg Glu Asp  Ser Asn Leu
    1205                1210                1215

gag tca  tct cag ttg act gtt  caa gca gaa ttt gat  atg tct gcc      3699
Glu Ser  Ser Gln Leu Thr Val  Gln Ala Glu Phe Asp  Met Ser Ala
    1220                1225                1230

ata cct  aga aaa cgt ggt aga  cca aga aaa atc aat  cca tct gaa      3744
Ile Pro  Arg Lys Arg Gly Arg  Pro Arg Lys Ile Asn  Pro Ser Glu
    1235                1240                1245

gat gta  gga tct aag gct gtt  aag gaa gag aga agc  ccc aag aag      3789
Asp Val  Gly Ser Lys Ala Val  Lys Glu Glu Arg Ser  Pro Lys Lys
    1250                1255                1260

aaa gaa  gct ccc agc att aga  agg aga tct aca aga  aat acc cca      3834
Lys Glu  Ala Pro Ser Ile Arg  Arg Arg Ser Thr Arg  Asn Thr Pro
    1265                1270                1275

gct aaa  agt gaa aat gtt gat  gtt gga aaa cca gct  tta gga aaa      3879
Ala Lys  Ser Glu Asn Val Asp  Val Gly Lys Pro Ala  Leu Gly Lys
    1280                1285                1290

tcc att  tta gtg cca aac gag  gaa ctt tcg atg gtg  atg agc tct      3924
Ser Ile  Leu Val Pro Asn Glu  Glu Leu Ser Met Val  Met Ser Ser
    1295                1300                1305

aag aaa  aaa ctt aca aaa aag  act gaa agt caa agc  caa aaa cgt      3969
Lys Lys  Lys Leu Thr Lys Lys  Thr Glu Ser Gln Ser  Gln Lys Arg
    1310                1315                1320

tca ttg  cac tca gta tca gaa  gaa cgc aca gat gaa  atg aca cat      4014
Ser Leu  His Ser Val Ser Glu  Glu Arg Thr Asp Glu  Met Thr His
    1325                1330                1335

aaa gaa  aca aat gag cag gaa  gaa aga ttg ctc gcc  aca gct tcc      4059
Lys Glu  Thr Asn Glu Gln Glu  Glu Arg Leu Leu Ala  Thr Ala Ser
    1340                1345                1350

ttc act  aaa tca tcc cgc agc  agc agg act cgg tct  agc aag gcc      4104
Phe Thr  Lys Ser Ser Arg Ser  Ser Arg Thr Arg Ser  Ser Lys Ala
    1355                1360                1365

atc ttg  ttg ccg gac ctt tct  gaa cca aac aat gag  cct tta ttt      4149
Ile Leu  Leu Pro Asp Leu Ser  Glu Pro Asn Asn Glu  Pro Leu Phe
    1370                1375                1380

tct cca  gcg tca gaa gtt cca  agg aaa gca aaa gct  aaa aaa ata      4194
Ser Pro  Ala Ser Glu Val Pro  Arg Lys Ala Lys Ala  Lys Lys Ile
    1385                1390                1395

gag gtt  cct gca cag ctg aaa  gaa tta gtt tcg gat  tta tct tct      4239
Glu Val  Pro Ala Gln Leu Lys  Glu Leu Val Ser Asp  Leu Ser Ser
    1400                1405                1410

cag ttt  gtc atc tca cct cct  gct tta agg agc aga  caa aaa aac      4284
Gln Phe  Val Ile Ser Pro Pro  Ala Leu Arg Ser Arg  Gln Lys Asn
    1415                1420                1425

aca tcc  aat aag aac aag ctt  gaa gat gaa ctg aaa  gat gat gca      4329
Thr Ser  Asn Lys Asn Lys Leu  Glu Asp Glu Leu Lys  Asp Asp Ala
    1430                1435                1440

caa tca  gta gaa act ctg gga  aag cca aaa gcg aaa  cga atc agg      4374
Gln Ser  Val Glu Thr Leu Gly  Lys Pro Lys Ala Lys  Arg Ile Arg
    1445                1450                1455

acg tca  aaa aca aaa caa gca  agc aaa aac aca gaa  aaa gaa agt      4419
Thr Ser  Lys Thr Lys Gln Ala  Ser Lys Asn Thr Glu  Lys Glu Ser
    1460                1465                1470

gct tgg  tca ctt cct ccc ata  gaa att cgg ctg att  tcc ccc ttg      4464
Ala Trp  Ser Leu Pro Pro Ile  Glu Ile Arg Leu Ile  Ser Pro Leu
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    1475                1480                1485

gct agc  cca gct gac gga gtc  aag agc aaa cca aga  aaa act aca      4509
Ala Ser  Pro Ala Asp Gly Val  Lys Ser Lys Pro Arg  Lys Thr Thr
    1490                1495                1500

gaa gtg  aca gga aca ggt ctt  gga agg aac aga aag  aaa ctg tct      4554
Glu Val  Thr Gly Thr Gly Leu  Gly Arg Asn Arg Lys  Lys Leu Ser
    1505                1510                1515

tcc tat  cca aag caa att tta  cgc aga aaa atg ctg  taatttcttg      4600
Ser Tyr  Pro Lys Gln Ile Leu  Arg Arg Lys Met Leu
    1520                1525                1530

ggaagatttt aatgtacacc tatttgtaaa gtcatcagaa tagtgtggat tattaaatat   4660

ctagtttgga agaaaataat ttatataaat tattgtaaat ttttatgtaa acagaaggtc   4720

ttcaataagt aaagtaactc catatggagt gattgtttca gtccaggcaa tttttctatt   4780

ttatattaag acttcataca tttatatatg taaatatggc ttattaatgg aatgttaaat   4840

aaaatgtata cttctcaaaa aaaaaaaaaa aaaaaaaaaa aaa                     4883


<210> SEQ ID NO 6
<211> LENGTH: 1530
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Lys Tyr Pro Pro
1               5                   10                  15

Ala Ser Leu His Ala Val Leu Asp Met Tyr Leu Leu Asp Gly Val Thr
            20                  25                  30

Glu Ala Ala Lys His Ser Ile Thr Ile Tyr Leu Leu Leu Asp Ile Met
        35                  40                  45

Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe Pro Thr
    50                  55                  60

Val Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Ile Gln Gly Phe Trp
65                  70                  75                  80

Leu Ile Asp His Asn Asp Tyr Glu Ser Gly Leu Asp Leu Leu Phe His
                85                  90                  95

Pro Ala Thr Ala Lys Pro Leu Ser Trp Gln His Ser Lys Ile Ile Gln
            100                 105                 110

Ala Phe Met Ser Gln Gly Glu His Arg Gln Ala Leu Arg Tyr Ile Gln
        115                 120                 125

Thr Met Lys Pro Thr Val Ser Ser Gly Asn Asp Val Ile Leu His Leu
    130                 135                 140

Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn Phe Leu
145                 150                 155                 160

Arg Gln His Cys Asn Arg Leu Asn Ile Glu Glu Leu Leu Lys His Met
                165                 170                 175

Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu Lys Leu
            180                 185                 190

Pro Phe Thr Asp Thr Glu Gln Glu Cys Leu Val Lys Phe Leu Gln Ser
        195                 200                 205

Ser Ala Ser Val Gln Asn His Glu Phe Leu Leu Val His His Leu Gln
    210                 215                 220

Arg Ala Asn Tyr Val Pro Ala Leu Lys Leu Asn Gln Thr Leu Lys Ile
225                 230                 235                 240

Asn Val Met Asn Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser Leu Ala
                245                 250                 255
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Arg Asn Ser Ile Leu Asp Gln Tyr Gly Lys Ile Leu Pro Arg Val His
            260                 265                 270

Arg Lys Leu Ala Ile Glu Arg Ala Lys Pro Tyr His Leu Ser Thr Ser
        275                 280                 285

Ser Val Phe Arg Leu Val Ser Arg Pro Lys Pro Leu Ser Ala Val Pro
    290                 295                 300

Lys Gln Val Val Thr Gly Thr Val Leu Thr Arg Ser Val Phe Ile Asn
305                 310                 315                 320

Asn Val Leu Ser Lys Ile Gly Glu Val Trp Ala Ser Lys Glu Pro Ile
                325                 330                 335

Asn Ser Thr Thr Pro Phe Asn Ser Ser Lys Ile Glu Glu Pro Ser Pro
            340                 345                 350

Ile Val Tyr Ser Leu Pro Ala Pro Glu Leu Pro Glu Ala Phe Phe Gly
        355                 360                 365

Thr Pro Ile Ser Lys Ala Ser Gln Lys Ile Ser Arg Leu Leu Asp Leu
    370                 375                 380

Val Val Gln Pro Val Pro Arg Pro Ser Gln Cys Ser Glu Phe Ile Gln
385                 390                 395                 400

Gln Ser Ser Met Lys Ser Pro Leu Tyr Leu Val Ser Arg Ser Leu Pro
                405                 410                 415

Ser Ser Ser Gln Leu Lys Gly Ser Pro Gln Ala Ile Ser Arg Ala Ser
            420                 425                 430

Glu Leu His Leu Leu Glu Thr Pro Leu Val Val Lys Lys Ala Lys Ser
        435                 440                 445

Leu Ala Met Ser Val Thr Thr Ser Gly Phe Ser Glu Phe Thr Pro Gln
    450                 455                 460

Ser Ile Leu Arg Ser Thr Pro Arg Ser Thr Pro Leu Ala Ser Pro Ser
465                 470                 475                 480

Pro Ser Pro Gly Arg Ser Pro Gln Arg Leu Lys Glu Thr Arg Ile Ser
                485                 490                 495

Phe Val Glu Glu Asp Val His Pro Lys Trp Ile Pro Gly Ala Ala Asp
            500                 505                 510

Asp Ser Lys Leu Glu Val Phe Thr Thr Pro Lys Lys Cys Ala Val Pro
        515                 520                 525

Val Glu Thr Glu Trp Pro Lys Ser Lys Asp Arg Thr Thr Ser Phe Phe
    530                 535                 540

Leu Asn Ser Pro Glu Lys Glu His Gln Glu Met Asp Glu Gly Ser Gln
545                 550                 555                 560

Ser Leu Glu Lys Leu Asp Val Ser Lys Gly Asn Ser Ser Val Ser Ile
                565                 570                 575

Thr Ser Asp Glu Thr Thr Leu Glu Tyr Gln Asp Ala Pro Ser Pro Glu
            580                 585                 590

Asp Leu Glu Glu Thr Val Phe Thr Ala Ser Lys Pro Lys Ser Ser Ser
        595                 600                 605

Thr Ala Leu Thr Thr Asn Val Thr Glu Gln Thr Glu Lys Asp Gly Asp
    610                 615                 620

Lys Asp Val Phe Ala Ser Glu Val Thr Pro Ser Asp Leu Gln Lys Gln
625                 630                 635                 640

Met Gly Asn Leu Glu Asp Ala Glu Thr Lys Asp Leu Leu Val Ala Ala
                645                 650                 655

Glu Ala Phe Ser Glu Leu Asn His Leu Ser Pro Val Gln Gly Thr Glu
            660                 665                 670

Ala Ser Leu Cys Ala Pro Ser Val Tyr Glu Gly Lys Ile Phe Thr Gln
        675                 680                 685
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Lys Ser Lys Val Pro Val Leu Asp Glu Gly Leu Thr Ser Val Glu Thr
    690                 695                 700

Tyr Thr Pro Ala Ile Arg Ala Asn Asp Asn Lys Ser Met Ala Asp Val
705                 710                 715                 720

Leu Gly Asp Gly Gly Asn Ser Ser Leu Thr Ile Ser Glu Gly Pro Ile
                725                 730                 735

Val Ser Glu Arg Arg Leu Asn Gln Glu Val Ala Leu Asn Leu Lys Glu
            740                 745                 750

Asp His Glu Val Glu Val Gly Val Leu Lys Glu Ser Val Asp Leu Pro
        755                 760                 765

Glu Glu Lys Leu Pro Ile Ser Asp Ser Pro Pro Asp Thr Gln Glu Ile
    770                 775                 780

His Val Ile Glu Gln Glu Lys Leu Glu Ala Gln Asp Ser Gly Glu Glu
785                 790                 795                 800

Ala Arg Asn Leu Ser Phe Asn Glu Leu Tyr Pro Ser Gly Thr Leu Lys
                805                 810                 815

Leu Gln Tyr Asn Phe Asp Thr Ile Asp Gln Gln Phe Cys Asp Leu Ala
            820                 825                 830

Asp Asn Lys Asp Thr Ala Glu Cys Asp Ile Ala Glu Val Asp Gly Glu
        835                 840                 845

Leu Phe Val Ala Gln Ser Asn Phe Thr Leu Ile Leu Glu Gly Glu Glu
    850                 855                 860

Gly Glu Val Glu Pro Gly Asp Phe Ala Ser Ser Asp Val Leu Pro Lys
865                 870                 875                 880

Ala Ala Asn Thr Ala Thr Glu Glu Lys Leu Val Cys Ser Gly Glu Asn
                885                 890                 895

Asp Asn His Gly Gln Ile Ala Asn Leu Pro Ser Ala Val Thr Ser Asp
            900                 905                 910

Gln Lys Ser Gln Lys Val Asp Thr Leu Pro Tyr Val Pro Glu Pro Ile
        915                 920                 925

Lys Val Ala Ile Ala Glu Asn Leu Leu Asp Val Ile Lys Asp Thr Arg
    930                 935                 940

Ser Lys Glu Ile Thr Ser Asp Thr Met Glu Gln Ser Ile His Glu Thr
945                 950                 955                 960

Ile Pro Leu Val Ser Gln Asn Ile Met Cys Pro Thr Lys Leu Val Lys
                965                 970                 975

Ser Ala Phe Lys Thr Ala Gln Glu Thr Ser Thr Met Thr Met Asn Val
            980                 985                 990

Ser Gln Val Asp Asp Val Val Ser  Ser Lys Thr Arg Thr  Arg Gly Gln
        995                 1000                1005

Arg Ile  Gln Asn Val Asn Val  Lys Ser Ala Gln Gln  Glu Ala Ser
    1010                1015                1020

Ala Asp  Val Ala Thr Pro Lys  Met Pro Gly Gln Ser  Val Arg Lys
    1025                1030                1035

Lys Thr  Arg Lys Ala Lys Glu  Ile Ser Glu Ala Ser  Glu Asn Ile
    1040                1045                1050

Tyr Ser  Asp Val Arg Gly Leu  Phe Gln Asn Gln Gln  Ile Pro Gln
    1055                1060                1065

Asn Ser  Val Thr Pro Arg Arg  Gly Arg Arg Lys Lys  Glu Val Asn
    1070                1075                1080

Gln Asp  Ile Leu Glu Asn Thr  Ser Ser Val Glu Gln  Glu Leu Gln
    1085                1090                1095

Ile Thr  Thr Gly Arg Glu Ser  Lys Arg Leu Lys Ser  Ser Gln Leu
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    1100                1105                1110

Leu Glu  Pro Ala Val Glu Glu  Thr Thr Lys Lys Glu  Val Lys Val
    1115                1120                1125

Ser Ser  Val Thr Lys Arg Thr  Pro Arg Arg Ile Lys  Arg Ser Val
    1130                1135                1140

Glu Asn  Gln Glu Ser Val Glu  Ile Ile Asn Asp Leu  Lys Val Ser
    1145                1150                1155

Thr Val  Thr Ser Pro Ser Arg  Met Ile Arg Lys Leu  Arg Ser Thr
    1160                1165                1170

Asn Leu  Asp Ala Ser Glu Asn  Thr Gly Asn Lys Gln  Asp Asp Lys
    1175                1180                1185

Ser Ser  Asp Lys Gln Leu Arg  Ile Lys His Val Arg  Arg Val Arg
    1190                1195                1200

Gly Arg  Glu Val Ser Pro Ser  Asp Val Arg Glu Asp  Ser Asn Leu
    1205                1210                1215

Glu Ser  Ser Gln Leu Thr Val  Gln Ala Glu Phe Asp  Met Ser Ala
    1220                1225                1230

Ile Pro  Arg Lys Arg Gly Arg  Pro Arg Lys Ile Asn  Pro Ser Glu
    1235                1240                1245

Asp Val  Gly Ser Lys Ala Val  Lys Glu Glu Arg Ser  Pro Lys Lys
    1250                1255                1260

Lys Glu  Ala Pro Ser Ile Arg  Arg Arg Ser Thr Arg  Asn Thr Pro
    1265                1270                1275

Ala Lys  Ser Glu Asn Val Asp  Val Gly Lys Pro Ala  Leu Gly Lys
    1280                1285                1290

Ser Ile  Leu Val Pro Asn Glu  Glu Leu Ser Met Val  Met Ser Ser
    1295                1300                1305

Lys Lys  Lys Leu Thr Lys Lys  Thr Glu Ser Gln Ser  Gln Lys Arg
    1310                1315                1320

Ser Leu  His Ser Val Ser Glu  Glu Arg Thr Asp Glu  Met Thr His
    1325                1330                1335

Lys Glu  Thr Asn Glu Gln Glu  Glu Arg Leu Leu Ala  Thr Ala Ser
    1340                1345                1350

Phe Thr  Lys Ser Ser Arg Ser  Ser Arg Thr Arg Ser  Ser Lys Ala
    1355                1360                1365

Ile Leu  Leu Pro Asp Leu Ser  Glu Pro Asn Asn Glu  Pro Leu Phe
    1370                1375                1380

Ser Pro  Ala Ser Glu Val Pro  Arg Lys Ala Lys Ala  Lys Lys Ile
    1385                1390                1395

Glu Val  Pro Ala Gln Leu Lys  Glu Leu Val Ser Asp  Leu Ser Ser
    1400                1405                1410

Gln Phe  Val Ile Ser Pro Pro  Ala Leu Arg Ser Arg  Gln Lys Asn
    1415                1420                1425

Thr Ser  Asn Lys Asn Lys Leu  Glu Asp Glu Leu Lys  Asp Asp Ala
    1430                1435                1440

Gln Ser  Val Glu Thr Leu Gly  Lys Pro Lys Ala Lys  Arg Ile Arg
    1445                1450                1455

Thr Ser  Lys Thr Lys Gln Ala  Ser Lys Asn Thr Glu  Lys Glu Ser
    1460                1465                1470

Ala Trp  Ser Leu Pro Pro Ile  Glu Ile Arg Leu Ile  Ser Pro Leu
    1475                1480                1485

Ala Ser  Pro Ala Asp Gly Val  Lys Ser Lys Pro Arg  Lys Thr Thr
    1490                1495                1500
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Glu Val  Thr Gly Thr Gly Leu  Gly Arg Asn Arg Lys  Lys Leu Ser
    1505                1510                1515

Ser Tyr  Pro Lys Gln Ile Leu  Arg Arg Lys Met Leu
    1520                1525                1530


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<211> LENGTH: 4115
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (2)..(3817)
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t

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  Gln Ile Leu Lys Asn Asn Leu Met Ser Asp Arg Asp Pro Arg Leu Arg
  1               5                  10                  15

gaa aga tcg gtg act cga aat tct ata tta gac cag tat ggg aaa atc      97
Glu Arg Ser Val Thr Arg Asn Ser Ile Leu Asp Gln Tyr Gly Lys Ile
            20                  25                  30

cta cct aga gtc cag aga aag tta gct gtt gag cga gct aag cct tac     145
Leu Pro Arg Val Gln Arg Lys Leu Ala Val Glu Arg Ala Lys Pro Tyr
        35                  40                  45

cac ctg tcg aca tcc tca gtt ttt cat gaa gtt tct aga ccc aaa ccg     193
His Leu Ser Thr Ser Ser Val Phe His Glu Val Ser Arg Pro Lys Pro
    50                  55                  60

tta tcg gca ttt cca aag aaa gct ata act gga aca gtg tta acc cga     241
Leu Ser Ala Phe Pro Lys Lys Ala Ile Thr Gly Thr Val Leu Thr Arg
65                  70                  75                  80

tct acg ttc atc agc aat gtt tta tct aaa att gga gag gtg tgg gca     289
Ser Thr Phe Ile Ser Asn Val Leu Ser Lys Ile Gly Glu Val Trp Ala
                85                  90                  95

agt cat gag cct aga aat ggc gtc tca ctt ttt aac agt cct aaa aca     337
Ser His Glu Pro Arg Asn Gly Val Ser Leu Phe Asn Ser Pro Lys Thr
            100                 105                 110

gaa cag cca tct cct gta gta cac tct ttc cca cac cca gag ctt cct     385
Glu Gln Pro Ser Pro Val Val His Ser Phe Pro His Pro Glu Leu Pro
        115                 120                 125

gag gcg ttt gtt gga act cca att tca aat aca tcc cag aga att tct     433
Glu Ala Phe Val Gly Thr Pro Ile Ser Asn Thr Ser Gln Arg Ile Ser
    130                 135                 140

aga tta ctg gat ttg gtt gtc cat cct gta ccc cag cct tct cag tgt     481
Arg Leu Leu Asp Leu Val Val His Pro Val Pro Gln Pro Ser Gln Cys
145                 150                 155                 160

ttg gag ttt att caa caa agt ccc aca aga tct cct ttg tgt ctg ctg     529
Leu Glu Phe Ile Gln Gln Ser Pro Thr Arg Ser Pro Leu Cys Leu Leu
                165                 170                 175

tcc agt tcg tta cca tta agt tca cag ttt aaa agg cca cat cag aat     577
Ser Ser Ser Leu Pro Leu Ser Ser Gln Phe Lys Arg Pro His Gln Asn
            180                 185                 190

acc tcc agg cct tca gag ttg ctt tta ctt gag act cct ctc ata gtt     625
Thr Ser Arg Pro Ser Glu Leu Leu Leu Leu Glu Thr Pro Leu Ile Val
        195                 200                 205

aag aaa gct aaa tct ttg gct ctg tca gcc acg tct tct gga ttt gcc     673
Lys Lys Ala Lys Ser Leu Ala Leu Ser Ala Thr Ser Ser Gly Phe Ala
    210                 215                 220

gag ttt act cct cca tcc atc ctt agg tct ggt ttt cga aca aca cct     721
Glu Phe Thr Pro Pro Ser Ile Leu Arg Ser Gly Phe Arg Thr Thr Pro
225                 230                 235                 240
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tta gca tct ccc tct ttg tca cct gga aga tct ctc act ccg cct ttc      769
Leu Ala Ser Pro Ser Leu Ser Pro Gly Arg Ser Leu Thr Pro Pro Phe
                245                 250                 255

aga gtt aaa gaa aca agg att tca ttc atg gaa gaa ggc atg aat aca      817
Arg Val Lys Glu Thr Arg Ile Ser Phe Met Glu Glu Gly Met Asn Thr
            260                 265                 270

cac tgg act gat aga gct aca gat gac cga aat aca aaa gcg ttt gtt      865
His Trp Thr Asp Arg Ala Thr Asp Asp Arg Asn Thr Lys Ala Phe Val
        275                 280                 285

agc aca tct ttc cat aaa tgt gga ctt cca gca gaa act gag tgg atg      913
Ser Thr Ser Phe His Lys Cys Gly Leu Pro Ala Glu Thr Glu Trp Met
    290                 295                 300

aag acc agt gat aag aat aca tat ttt cct ctg gat gtc cct gca aag      961
Lys Thr Ser Asp Lys Asn Thr Tyr Phe Pro Leu Asp Val Pro Ala Lys
305                 310                 315                 320

ggc cct cag aaa gtg gtg gca gag tca ctg gct acc cat tca gga agg     1009
Gly Pro Gln Lys Val Val Ala Glu Ser Leu Ala Thr His Ser Gly Arg
                325                 330                 335

ctg gag aaa ctg gat gtg agc aaa gaa gac agc aca gct tcc acc agg     1057
Leu Glu Lys Leu Asp Val Ser Lys Glu Asp Ser Thr Ala Ser Thr Arg
            340                 345                 350

tca gac cag acc tcc tta gag tat cat gac gca cca tca cca gaa gac     1105
Ser Asp Gln Thr Ser Leu Glu Tyr His Asp Ala Pro Ser Pro Glu Asp
        355                 360                 365

ttg gaa ggt gct gtt ttt gtg tct ccc aag cca gca tct tcc tcc act     1153
Leu Glu Gly Ala Val Phe Val Ser Pro Lys Pro Ala Ser Ser Ser Thr
    370                 375                 380

gaa cta act act aat tca act cta caa aca gag agg gat aat gat aaa     1201
Glu Leu Thr Thr Asn Ser Thr Leu Gln Thr Glu Arg Asp Asn Asp Lys
385                 390                 395                 400

gat gcg ttt aag tca gaa ggt act cct tca ccc gtg aag aaa caa ata     1249
Asp Ala Phe Lys Ser Glu Gly Thr Pro Ser Pro Val Lys Lys Gln Ile
                405                 410                 415

ggc acg gga gac gct gca gtg gaa gca ttt tca gaa ctg agt cgc tta     1297
Gly Thr Gly Asp Ala Ala Val Glu Ala Phe Ser Glu Leu Ser Arg Leu
            420                 425                 430

gac cct gtt gaa aga gct gaa gct tct ttt ggt gtg tcg tca gtc tgt     1345
Asp Pro Val Glu Arg Ala Glu Ala Ser Phe Gly Val Ser Ser Val Cys
        435                 440                 445

gaa ggg gaa acc tcc act tca aac tcc aag acg tca gtt ctg gat gga     1393
Glu Gly Glu Thr Ser Thr Ser Asn Ser Lys Thr Ser Val Leu Asp Gly
    450                 455                 460

atc gtg cct att gag agc cga acc tcc ata ctt aca gca gac cac aaa     1441
Ile Val Pro Ile Glu Ser Arg Thr Ser Ile Leu Thr Ala Asp His Lys
465                 470                 475                 480

gag tct gtg gcc aac acg gtt gca gat gtt gaa agc tct ggg tcc acc     1489
Glu Ser Val Ala Asn Thr Val Ala Asp Val Glu Ser Ser Gly Ser Thr
                485                 490                 495

agc tcc aag tgc ccg gtt acc tct gaa cgc agc ctc ggc caa aaa cta     1537
Ser Ser Lys Cys Pro Val Thr Ser Glu Arg Ser Leu Gly Gln Lys Leu
            500                 505                 510

aca tta aac tta aaa gaa gat gaa ata gaa gct cat gta cca aag gag     1585
Thr Leu Asn Leu Lys Glu Asp Glu Ile Glu Ala His Val Pro Lys Glu
        515                 520                 525

aac gtt ggt tta cca gaa gaa agc cct cga att tct gct gct cct tct     1633
Asn Val Gly Leu Pro Glu Glu Ser Pro Arg Ile Ser Ala Ala Pro Ser
    530                 535                 540

gat act cac gag att cat cta att gga tgt gaa aat ctt gaa gtt caa     1681
Asp Thr His Glu Ile His Leu Ile Gly Cys Glu Asn Leu Glu Val Gln
545                 550                 555                 560
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aat tca gaa gag gag gcc aag aat ctt tca ttt gat gag ttg tat ccc     1729
Asn Ser Glu Glu Glu Ala Lys Asn Leu Ser Phe Asp Glu Leu Tyr Pro
                565                 570                 575

tta ggg gca gag aaa ctt gag tat aat ctc agt act att gag cag cag     1777
Leu Gly Ala Glu Lys Leu Glu Tyr Asn Leu Ser Thr Ile Glu Gln Gln
            580                 585                 590

ttt tgt gac ttg cct gat gac aaa gac tct gct gaa tgt gat gct gct     1825
Phe Cys Asp Leu Pro Asp Asp Lys Asp Ser Ala Glu Cys Asp Ala Ala
        595                 600                 605

gaa gta gac ggg gaa ctt ttt gtg gcc cag agc aac ttt acc ctg att     1873
Glu Val Asp Gly Glu Leu Phe Val Ala Gln Ser Asn Phe Thr Leu Ile
    610                 615                 620

tta gaa ggt gaa gaa gga gaa gct gag gca agc gac tct gca gca cct     1921
Leu Glu Gly Glu Glu Gly Glu Ala Glu Ala Ser Asp Ser Ala Ala Pro
625                 630                 635                 640

aat atg tta ccg aaa tcg acc aag gaa aaa cct gtg tgc tac agg gaa     1969
Asn Met Leu Pro Lys Ser Thr Lys Glu Lys Pro Val Cys Tyr Arg Glu
                645                 650                 655

ccc cat aat cag gag cgc gtt aca gat ttg cca tct gct gtg act gct     2017
Pro His Asn Gln Glu Arg Val Thr Asp Leu Pro Ser Ala Val Thr Ala
            660                 665                 670

gac caa gaa tcc cac aag gta gag act tta ccg tat gtg cct gaa ccg     2065
Asp Gln Glu Ser His Lys Val Glu Thr Leu Pro Tyr Val Pro Glu Pro
        675                 680                 685

gtt aaa gtg gca att gca gaa aat ctg ttg gat gta att aaa gac acc     2113
Val Lys Val Ala Ile Ala Glu Asn Leu Leu Asp Val Ile Lys Asp Thr
    690                 695                 700

aga agt aag gaa gca act ccc gtg gca gca ggt gag gct ggt gat gag     2161
Arg Ser Lys Glu Ala Thr Pro Val Ala Ala Gly Glu Ala Gly Asp Glu
705                 710                 715                 720

gac gga gca gtg ata gtc tca aag gct gca cat tcg tcc agg ctg aca     2209
Asp Gly Ala Val Ile Val Ser Lys Ala Ala His Ser Ser Arg Leu Thr
                725                 730                 735

aac tct aca ccg aag act gtt aag gaa cca cgt gca gag act gta aat     2257
Asn Ser Thr Pro Lys Thr Val Lys Glu Pro Arg Ala Glu Thr Val Asn
            740                 745                 750

acc agc cag agt gat gac atg gtt tct tct aga act ctc aca aga agg     2305
Thr Ser Gln Ser Asp Asp Met Val Ser Ser Arg Thr Leu Thr Arg Arg
        755                 760                 765

cag cat gcc cta agc ctg aat gtc aca tca gaa caa gag cct tca gca     2353
Gln His Ala Leu Ser Leu Asn Val Thr Ser Glu Gln Glu Pro Ser Ala
    770                 775                 780

gtt gcc act cct aag aag aga act aga aaa att aaa gaa act cct gag     2401
Val Ala Thr Pro Lys Lys Arg Thr Arg Lys Ile Lys Glu Thr Pro Glu
785                 790                 795                 800

tct tct gaa agg acc tgt tct gac cta aaa gta gca cct gag aac caa     2449
Ser Ser Glu Arg Thr Cys Ser Asp Leu Lys Val Ala Pro Glu Asn Gln
                805                 810                 815

ctg aca gct cag aat cct ccc gct cct agg aga aga aag aag aag gac     2497
Leu Thr Ala Gln Asn Pro Pro Ala Pro Arg Arg Arg Lys Lys Lys Asp
            820                 825                 830

gtt agc caa ggc aca ctg cca agt tct ggt gct gtg gag ccg gag ccg     2545
Val Ser Gln Gly Thr Leu Pro Ser Ser Gly Ala Val Glu Pro Glu Pro
        835                 840                 845

gaa cct cag ggt acg ccg gga aga ctg agg ctg aga acg cag cca ccc     2593
Glu Pro Gln Gly Thr Pro Gly Arg Leu Arg Leu Arg Thr Gln Pro Pro
    850                 855                 860

gag cca gca gct gaa gaa act cct tct aga aca aaa gtc agg ctt tca     2641
Glu Pro Ala Ala Glu Glu Thr Pro Ser Arg Thr Lys Val Arg Leu Ser
865                 870                 875                 880
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tct gtt aga aag gga acc cct aga aga ctt aag aag tct gta gaa aat     2689
Ser Val Arg Lys Gly Thr Pro Arg Arg Leu Lys Lys Ser Val Glu Asn
                885                 890                 895

ggg caa agt ata gaa att cta gat gat ctc aaa ggg agt gag gca gca     2737
Gly Gln Ser Ile Glu Ile Leu Asp Asp Leu Lys Gly Ser Glu Ala Ala
            900                 905                 910

agt cat gac ggg act gtc aca gag ctg agg aat gcc aat tta gaa gat     2785
Ser His Asp Gly Thr Val Thr Glu Leu Arg Asn Ala Asn Leu Glu Asp
        915                 920                 925

act cag aat atg gag tat aaa caa gat gaa cac agt gac cag caa ccg     2833
Thr Gln Asn Met Glu Tyr Lys Gln Asp Glu His Ser Asp Gln Gln Pro
    930                 935                 940

cct cta aaa cga aag agg gtc aga gag aga gaa gtt agt gtg tca agt     2881
Pro Leu Lys Arg Lys Arg Val Arg Glu Arg Glu Val Ser Val Ser Ser
945                 950                 955                 960

gtg aca gaa gag cca aag ctt gac tca tcc cag ttg cct ctt cag aca     2929
Val Thr Glu Glu Pro Lys Leu Asp Ser Ser Gln Leu Pro Leu Gln Thr
                965                 970                 975

gga ctc gat gta cct gcc acc cct agg aaa cgt ggt aga ccc agg aag     2977
Gly Leu Asp Val Pro Ala Thr Pro Arg Lys Arg Gly Arg Pro Arg Lys
            980                 985                 990

gta gtt ccc tta gaa gct gac ggt  ggc aca act ggt aag  gaa cag aca   3025
Val Val Pro Leu Glu Ala Asp Gly  Gly Thr Thr Gly Lys  Glu Gln Thr
        995                 1000                1005

agt cct  cag aag aaa gat gtt  ccg gtt gtc cgg aga  tct aca cgg      3070
Ser Pro  Gln Lys Lys Asp Val  Pro Val Val Arg Arg  Ser Thr Arg
    1010                1015                1020

aac acc  cca gct aga aat gtg  agt act tta naa aaa  tca gtt tta      3115
Asn Thr  Pro Ala Arg Asn Val  Ser Thr Leu Xaa Lys  Ser Val Leu
    1025                1030                1035

gtg cca  aat aag gaa gct gct  cta gtg gtg aca tct  aag agg aga      3160
Val Pro  Asn Lys Glu Ala Ala  Leu Val Val Thr Ser  Lys Arg Arg
    1040                1045                1050

cct aca  aag aag tct gca gag  gaa agc tca aaa gat  cca tca gcg      3205
Pro Thr  Lys Lys Ser Ala Glu  Glu Ser Ser Lys Asp  Pro Ser Ala
    1055                1060                1065

gca gtc  tca gac tgg gcg ggt  gga gca gcc cac aca  gag tcc gct      3250
Ala Val  Ser Asp Trp Ala Gly  Gly Ala Ala His Thr  Glu Ser Ala
    1070                1075                1080

gac cga  agg gac gga ctg ctt  gcc gcc gct gct ctc  acg cca tct      3295
Asp Arg  Arg Asp Gly Leu Leu  Ala Ala Ala Ala Leu  Thr Pro Ser
    1085                1090                1095

gcc cag  ggc aca agg act agg  tct aga agg acc atg  ttg ttg acg      3340
Ala Gln  Gly Thr Arg Thr Arg  Ser Arg Arg Thr Met  Leu Leu Thr
    1100                1105                1110

gac att  tct gaa ccc aaa act  gag cct tta ttt cct  cct cct tca      3385
Asp Ile  Ser Glu Pro Lys Thr  Glu Pro Leu Phe Pro  Pro Pro Ser
    1115                1120                1125

gtg aag  gtt cca aag aaa aaa  tca aaa gct gag aac  atg gag gcc      3430
Val Lys  Val Pro Lys Lys Lys  Ser Lys Ala Glu Asn  Met Glu Ala
    1130                1135                1140

gca gcc  cag ctg aaa gaa ttg  gtg tca gat tta tct  tct cag ttt      3475
Ala Ala  Gln Leu Lys Glu Leu  Val Ser Asp Leu Ser  Ser Gln Phe
    1145                1150                1155

gtt gtt  tcc cct cct gcc ttg  aga acc agg cag aaa  agt ata tcc      3520
Val Val  Ser Pro Pro Ala Leu  Arg Thr Arg Gln Lys  Ser Ile Ser
    1160                1165                1170

aat act  tcc aag ctt cta ggt  gaa ctg gag agt gac  cct aaa cca      3565
Asn Thr  Ser Lys Leu Leu Gly  Glu Leu Glu Ser Asp  Pro Lys Pro
    1175                1180                1185
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tta gag  atc ata gaa caa aaa  cca aaa aga agc agg  act gtg aag      3610
Leu Glu  Ile Ile Glu Gln Lys  Pro Lys Arg Ser Arg  Thr Val Lys
    1190                1195                1200

aca aga  gca agc aga aac aca  gga aaa gga agt tct  tgg tca cct      3655
Thr Arg  Ala Ser Arg Asn Thr  Gly Lys Gly Ser Ser  Trp Ser Pro
    1205                1210                1215

cct cct  gta gaa att aag ctg  gtt tct ccc ttg gcg  agt cca gtg      3700
Pro Pro  Val Glu Ile Lys Leu  Val Ser Pro Leu Ala  Ser Pro Val
    1220                1225                1230

gat gaa  ata aag acc ggc aag  cca aga aaa act gca  gaa ata gca      3745
Asp Glu  Ile Lys Thr Gly Lys  Pro Arg Lys Thr Ala  Glu Ile Ala
    1235                1240                1245

gga aaa  act ctt gga agg ggc  aga aag aag cca tct  tct ttt cca      3790
Gly Lys  Thr Leu Gly Arg Gly  Arg Lys Lys Pro Ser  Ser Phe Pro
    1250                1255                1260

aag caa  att tta cgc agg aaa  atg ctg taatttttag cccaagattt        3837
Lys Gln  Ile Leu Arg Arg Lys  Met Leu
    1265                1270

taacacgcac ctgtttgtaa aagtcaacag tatttgtgtg gattattaaa gtcaccaatt   3897

tggatgaaaa tactttatat aaattgtaca attttgtaag cagtaaatga gtaactccac   3957

atggagtgca gttcttgtag tgcaggcgtt ttatacgact tgatgcgttt atatcaatgt   4017

aaatatgact tatcattggg aggttaaata aactactgta aagtaaaaaa aaaaaaaaaa   4077

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa                          4115


<210> SEQ ID NO 8
<211> LENGTH: 1272
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1034)..(1034)
<223> OTHER INFORMATION: The 'Xaa' at location 1034 stands for Lys, Glu,
      or Gln.

<400> SEQUENCE: 8

Gln Ile Leu Lys Asn Asn Leu Met Ser Asp Arg Asp Pro Arg Leu Arg
1               5                  10                  15

Glu Arg Ser Val Thr Arg Asn Ser Ile Leu Asp Gln Tyr Gly Lys Ile
            20                  25                  30

Leu Pro Arg Val Gln Arg Lys Leu Ala Val Glu Arg Ala Lys Pro Tyr
        35                  40                  45

His Leu Ser Thr Ser Ser Val Phe His Glu Val Ser Arg Pro Lys Pro
    50                  55                  60

Leu Ser Ala Phe Pro Lys Lys Ala Ile Thr Gly Thr Val Leu Thr Arg
65                  70                  75                  80

Ser Thr Phe Ile Ser Asn Val Leu Ser Lys Ile Gly Glu Val Trp Ala
                85                  90                  95

Ser His Glu Pro Arg Asn Gly Val Ser Leu Phe Asn Ser Pro Lys Thr
            100                 105                 110

Glu Gln Pro Ser Pro Val Val His Ser Phe Pro His Pro Glu Leu Pro
        115                 120                 125

Glu Ala Phe Val Gly Thr Pro Ile Ser Asn Thr Ser Gln Arg Ile Ser
    130                 135                 140

Arg Leu Leu Asp Leu Val Val His Pro Val Pro Gln Pro Ser Gln Cys
145                 150                 155                 160

Leu Glu Phe Ile Gln Gln Ser Pro Thr Arg Ser Pro Leu Cys Leu Leu
                165                 170                 175
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Ser Ser Ser Leu Pro Leu Ser Ser Gln Phe Lys Arg Pro His Gln Asn
            180                 185                 190

Thr Ser Arg Pro Ser Glu Leu Leu Leu Leu Glu Thr Pro Leu Ile Val
        195                 200                 205

Lys Lys Ala Lys Ser Leu Ala Leu Ser Ala Thr Ser Ser Gly Phe Ala
    210                 215                 220

Glu Phe Thr Pro Pro Ser Ile Leu Arg Ser Gly Phe Arg Thr Thr Pro
225                 230                 235                 240

Leu Ala Ser Pro Ser Leu Ser Pro Gly Arg Ser Leu Thr Pro Pro Phe
                245                 250                 255

Arg Val Lys Glu Thr Arg Ile Ser Phe Met Glu Glu Gly Met Asn Thr
            260                 265                 270

His Trp Thr Asp Arg Ala Thr Asp Asp Arg Asn Thr Lys Ala Phe Val
        275                 280                 285

Ser Thr Ser Phe His Lys Cys Gly Leu Pro Ala Glu Thr Glu Trp Met
    290                 295                 300

Lys Thr Ser Asp Lys Asn Thr Tyr Phe Pro Leu Asp Val Pro Ala Lys
305                 310                 315                 320

Gly Pro Gln Lys Val Val Ala Glu Ser Leu Ala Thr His Ser Gly Arg
                325                 330                 335

Leu Glu Lys Leu Asp Val Ser Lys Glu Asp Ser Thr Ala Ser Thr Arg
            340                 345                 350

Ser Asp Gln Thr Ser Leu Glu Tyr His Asp Ala Pro Ser Pro Glu Asp
        355                 360                 365

Leu Glu Gly Ala Val Phe Val Ser Pro Lys Pro Ala Ser Ser Ser Thr
    370                 375                 380

Glu Leu Thr Thr Asn Ser Thr Leu Gln Thr Glu Arg Asp Asn Asp Lys
385                 390                 395                 400

Asp Ala Phe Lys Ser Glu Gly Thr Pro Ser Pro Val Lys Lys Gln Ile
                405                 410                 415

Gly Thr Gly Asp Ala Ala Val Glu Ala Phe Ser Glu Leu Ser Arg Leu
            420                 425                 430

Asp Pro Val Glu Arg Ala Glu Ala Ser Phe Gly Val Ser Ser Val Cys
        435                 440                 445

Glu Gly Glu Thr Ser Thr Ser Asn Ser Lys Thr Ser Val Leu Asp Gly
    450                 455                 460

Ile Val Pro Ile Glu Ser Arg Thr Ser Ile Leu Thr Ala Asp His Lys
465                 470                 475                 480

Glu Ser Val Ala Asn Thr Val Ala Asp Val Glu Ser Ser Gly Ser Thr
                485                 490                 495

Ser Ser Lys Cys Pro Val Thr Ser Glu Arg Ser Leu Gly Gln Lys Leu
            500                 505                 510

Thr Leu Asn Leu Lys Glu Asp Glu Ile Glu Ala His Val Pro Lys Glu
        515                 520                 525

Asn Val Gly Leu Pro Glu Glu Ser Pro Arg Ile Ser Ala Ala Pro Ser
    530                 535                 540

Asp Thr His Glu Ile His Leu Ile Gly Cys Glu Asn Leu Glu Val Gln
545                 550                 555                 560

Asn Ser Glu Glu Glu Ala Lys Asn Leu Ser Phe Asp Glu Leu Tyr Pro
                565                 570                 575

Leu Gly Ala Glu Lys Leu Glu Tyr Asn Leu Ser Thr Ile Glu Gln Gln
            580                 585                 590

Phe Cys Asp Leu Pro Asp Asp Lys Asp Ser Ala Glu Cys Asp Ala Ala
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        595                 600                 605

Glu Val Asp Gly Glu Leu Phe Val Ala Gln Ser Asn Phe Thr Leu Ile
    610                 615                 620

Leu Glu Gly Glu Glu Gly Glu Ala Glu Ala Ser Asp Ser Ala Ala Pro
625                 630                 635                 640

Asn Met Leu Pro Lys Ser Thr Lys Glu Lys Pro Val Cys Tyr Arg Glu
                645                 650                 655

Pro His Asn Gln Glu Arg Val Thr Asp Leu Pro Ser Ala Val Thr Ala
            660                 665                 670

Asp Gln Glu Ser His Lys Val Glu Thr Leu Pro Tyr Val Pro Glu Pro
        675                 680                 685

Val Lys Val Ala Ile Ala Glu Asn Leu Leu Asp Val Ile Lys Asp Thr
    690                 695                 700

Arg Ser Lys Glu Ala Thr Pro Val Ala Ala Gly Glu Ala Gly Asp Glu
705                 710                 715                 720

Asp Gly Ala Val Ile Val Ser Lys Ala Ala His Ser Ser Arg Leu Thr
                725                 730                 735

Asn Ser Thr Pro Lys Thr Val Lys Glu Pro Arg Ala Glu Thr Val Asn
            740                 745                 750

Thr Ser Gln Ser Asp Asp Met Val Ser Ser Arg Thr Leu Thr Arg Arg
        755                 760                 765

Gln His Ala Leu Ser Leu Asn Val Thr Ser Glu Gln Glu Pro Ser Ala
    770                 775                 780

Val Ala Thr Pro Lys Lys Arg Thr Arg Lys Ile Lys Glu Thr Pro Glu
785                 790                 795                 800

Ser Ser Glu Arg Thr Cys Ser Asp Leu Lys Val Ala Pro Glu Asn Gln
                805                 810                 815

Leu Thr Ala Gln Asn Pro Pro Ala Pro Arg Arg Arg Lys Lys Lys Asp
            820                 825                 830

Val Ser Gln Gly Thr Leu Pro Ser Ser Gly Ala Val Glu Pro Glu Pro
        835                 840                 845

Glu Pro Gln Gly Thr Pro Gly Arg Leu Arg Leu Arg Thr Gln Pro Pro
    850                 855                 860

Glu Pro Ala Ala Glu Glu Thr Pro Ser Arg Thr Lys Val Arg Leu Ser
865                 870                 875                 880

Ser Val Arg Lys Gly Thr Pro Arg Arg Leu Lys Lys Ser Val Glu Asn
                885                 890                 895

Gly Gln Ser Ile Glu Ile Leu Asp Asp Leu Lys Gly Ser Glu Ala Ala
            900                 905                 910

Ser His Asp Gly Thr Val Thr Glu Leu Arg Asn Ala Asn Leu Glu Asp
        915                 920                 925

Thr Gln Asn Met Glu Tyr Lys Gln Asp Glu His Ser Asp Gln Gln Pro
    930                 935                 940

Pro Leu Lys Arg Lys Arg Val Arg Glu Arg Glu Val Ser Val Ser Ser
945                 950                 955                 960

Val Thr Glu Glu Pro Lys Leu Asp Ser Ser Gln Leu Pro Leu Gln Thr
                965                 970                 975

Gly Leu Asp Val Pro Ala Thr Pro Arg Lys Arg Gly Arg Pro Arg Lys
            980                 985                 990

Val Val Pro Leu Glu Ala Asp Gly  Gly Thr Thr Gly Lys  Glu Gln Thr
        995                 1000                1005

Ser Pro  Gln Lys Lys Asp Val  Pro Val Val Arg Arg  Ser Thr Arg
    1010                1015                1020
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Asn Thr  Pro Ala Arg Asn Val  Ser Thr Leu Xaa Lys  Ser Val Leu
    1025                1030                1035

Val Pro  Asn Lys Glu Ala Ala  Leu Val Val Thr Ser  Lys Arg Arg
    1040                1045                1050

Pro Thr  Lys Lys Ser Ala Glu  Glu Ser Ser Lys Asp  Pro Ser Ala
    1055                1060                1065

Ala Val  Ser Asp Trp Ala Gly  Gly Ala Ala His Thr  Glu Ser Ala
    1070                1075                1080

Asp Arg  Arg Asp Gly Leu Leu  Ala Ala Ala Ala Leu  Thr Pro Ser
    1085                1090                1095

Ala Gln  Gly Thr Arg Thr Arg  Ser Arg Arg Thr Met  Leu Leu Thr
    1100                1105                1110

Asp Ile  Ser Glu Pro Lys Thr  Glu Pro Leu Phe Pro  Pro Pro Ser
    1115                1120                1125

Val Lys  Val Pro Lys Lys Lys  Ser Lys Ala Glu Asn  Met Glu Ala
    1130                1135                1140

Ala Ala  Gln Leu Lys Glu Leu  Val Ser Asp Leu Ser  Ser Gln Phe
    1145                1150                1155

Val Val  Ser Pro Pro Ala Leu  Arg Thr Arg Gln Lys  Ser Ile Ser
    1160                1165                1170

Asn Thr  Ser Lys Leu Leu Gly  Glu Leu Glu Ser Asp  Pro Lys Pro
    1175                1180                1185

Leu Glu  Ile Ile Glu Gln Lys  Pro Lys Arg Ser Arg  Thr Val Lys
    1190                1195                1200

Thr Arg  Ala Ser Arg Asn Thr  Gly Lys Gly Ser Ser  Trp Ser Pro
    1205                1210                1215

Pro Pro  Val Glu Ile Lys Leu  Val Ser Pro Leu Ala  Ser Pro Val
    1220                1225                1230

Asp Glu  Ile Lys Thr Gly Lys  Pro Arg Lys Thr Ala  Glu Ile Ala
    1235                1240                1245

Gly Lys  Thr Leu Gly Arg Gly  Arg Lys Lys Pro Ser  Ser Phe Pro
    1250                1255                1260

Lys Gln  Ile Leu Arg Arg Lys  Met Leu
    1265                1270


<210> SEQ ID NO 9
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Primer Sequence

<400> SEQUENCE: 9

cacccgtgaa gaaacaaata ggca                                          24


<210> SEQ ID NO 10
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:Artificially
      Synthesized Primer Sequence

<400> SEQUENCE: 10

cctttggtac atgagcttct attt                                          24


<210> SEQ ID NO 11
<211> LENGTH: 7034
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<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (8)..(6736)

<400> SEQUENCE: 11

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tggcagt atg caa gac ttg aca gct caa gtg act agt gat ctc ctg cat       49
       Met Gln Asp Leu Thr Ala Gln Val Thr Ser Asp Leu Leu His
       1               5                   10

ttc cca gaa gtg act att gaa gct ctt gga gaa gat gag ata aca tta       97
Phe Pro Glu Val Thr Ile Glu Ala Leu Gly Glu Asp Glu Ile Thr Leu
15                  20                  25                  30

gag tcc gtg ctt cgt gga aag ttt gct gca ggg aaa aat gga cta gca      145
Glu Ser Val Leu Arg Gly Lys Phe Ala Ala Gly Lys Asn Gly Leu Ala
                35                  40                  45

tgc tta gct tgt ggt cca caa ctt gaa gtt gta aac tcc tta aca gga      193
Cys Leu Ala Cys Gly Pro Gln Leu Glu Val Val Asn Ser Leu Thr Gly
            50                  55                  60

gag cgg tta tct gca tat aga ttc agt gga gta aat gaa cag cct cct      241
Glu Arg Leu Ser Ala Tyr Arg Phe Ser Gly Val Asn Glu Gln Pro Pro
        65                  70                  75

gta gtc ctt gca gtg aaa gaa ttc tct tgg cat aag agg act gga ttg      289
Val Val Leu Ala Val Lys Glu Phe Ser Trp His Lys Arg Thr Gly Leu
    80                  85                  90

tta ata gga ttg gaa gaa gca gat ggg agt gtt ctt tgt ctt tat gac      337
Leu Ile Gly Leu Glu Glu Ala Asp Gly Ser Val Leu Cys Leu Tyr Asp
95                  100                 105                 110

ctt ggt ata tca aga gtg gtc aaa gca gtt gtt ctt cct gga agg gta      385
Leu Gly Ile Ser Arg Val Val Lys Ala Val Val Leu Pro Gly Arg Val
                115                 120                 125

aca gct atc gag cct ata att aac cat gga gga gcc agt gcg agt acc      433
Thr Ala Ile Glu Pro Ile Ile Asn His Gly Gly Ala Ser Ala Ser Thr
            130                 135                 140

cag cat tta cat cca agt ctc cgg tgg ctt ttt ggc gtg gcc gct gtg      481
Gln His Leu His Pro Ser Leu Arg Trp Leu Phe Gly Val Ala Ala Val
        145                 150                 155

gtg act gat gtt gga cag atc ctt ctt att gac ctg tgt ttg gat gac      529
Val Thr Asp Val Gly Gln Ile Leu Leu Ile Asp Leu Cys Leu Asp Asp
    160                 165                 170

ttg tcc tgc agt cag aat gaa gtt gag gca tca gac ctt gaa gtt atc      577
Leu Ser Cys Ser Gln Asn Glu Val Glu Ala Ser Asp Leu Glu Val Ile
175                 180                 185                 190

act ggt atc cca gct gaa gta cca cac atc aga gag aga gtg atg aga      625
Thr Gly Ile Pro Ala Glu Val Pro His Ile Arg Glu Arg Val Met Arg
                195                 200                 205

gag ggg cgc cac ctg tgc ttc cag tta gta agc cca ttg gga gta gcc      673
Glu Gly Arg His Leu Cys Phe Gln Leu Val Ser Pro Leu Gly Val Ala
            210                 215                 220

att tct act ctg agt tac atc aac agg aca aat cag ctt gct gtg ggt      721
Ile Ser Thr Leu Ser Tyr Ile Asn Arg Thr Asn Gln Leu Ala Val Gly
        225                 230                 235

ttt tct gat ggc tac tta gca ctt tgg aac atg aaa agc atg aaa aga      769
Phe Ser Asp Gly Tyr Leu Ala Leu Trp Asn Met Lys Ser Met Lys Arg
    240                 245                 250

gaa tac tat aca cag ttg gaa ggt gga agg gtt cct gtc cat gca gtt      817
Glu Tyr Tyr Thr Gln Leu Glu Gly Gly Arg Val Pro Val His Ala Val
255                 260                 265                 270

gcc ttt caa gag cct gag aat gat cct cgt aac tgc tgt tat tta tgg      865
Ala Phe Gln Glu Pro Glu Asn Asp Pro Arg Asn Cys Cys Tyr Leu Trp
                275                 280                 285
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gct gtt cag tcc aca caa gat agt gaa ggg gat gtt ttg agt ttg cat      913
Ala Val Gln Ser Thr Gln Asp Ser Glu Gly Asp Val Leu Ser Leu His
            290                 295                 300

ctg ctt cag ctg gct ttt ggt gat aga aaa tgt ttg gca tca ggg caa      961
Leu Leu Gln Leu Ala Phe Gly Asp Arg Lys Cys Leu Ala Ser Gly Gln
        305                 310                 315

att tta tat gag gga tta gaa tac tgc gaa gaa aga tat aca ctg gat     1009
Ile Leu Tyr Glu Gly Leu Glu Tyr Cys Glu Glu Arg Tyr Thr Leu Asp
    320                 325                 330

cta gca ggt ggc acg ttc ccc tta agg gga caa act agt aat acc aaa     1057
Leu Ala Gly Gly Thr Phe Pro Leu Arg Gly Gln Thr Ser Asn Thr Lys
335                 340                 345                 350

ttg ttg gga tgc cag agt ata gag aga ttt cca tct cat gga gac aga     1105
Leu Leu Gly Cys Gln Ser Ile Glu Arg Phe Pro Ser His Gly Asp Arg
                355                 360                 365

gaa gaa agt atg aga gaa gct ctg tct ccc gat acc agc gtt tct gtc     1153
Glu Glu Ser Met Arg Glu Ala Leu Ser Pro Asp Thr Ser Val Ser Val
            370                 375                 380

ttt acc tgg caa gtg aat ata tat gga cag gga aag cct tct gtg tat     1201
Phe Thr Trp Gln Val Asn Ile Tyr Gly Gln Gly Lys Pro Ser Val Tyr
        385                 390                 395

tta ggg cta ttt gac ata aat cgt tgg tat cat gca caa atg ccc gat     1249
Leu Gly Leu Phe Asp Ile Asn Arg Trp Tyr His Ala Gln Met Pro Asp
    400                 405                 410

tct tta aga tca gga gaa tct ctg cat aat tgc tct tat ttt gcg ttg     1297
Ser Leu Arg Ser Gly Glu Ser Leu His Asn Cys Ser Tyr Phe Ala Leu
415                 420                 425                 430

tgg tca ttg gat tcg gtt gta agt agg act tct cca cat cac atc ttg     1345
Trp Ser Leu Asp Ser Val Val Ser Arg Thr Ser Pro His His Ile Leu
                435                 440                 445

gac ata cta gta cat gag agg agt tta aac cga ggg gtt cct cct tcc     1393
Asp Ile Leu Val His Glu Arg Ser Leu Asn Arg Gly Val Pro Pro Ser
            450                 455                 460

tac cca cct cca gag caa ttt ttt aac cca agt act ttt aat ttt gat     1441
Tyr Pro Pro Pro Glu Gln Phe Phe Asn Pro Ser Thr Phe Asn Phe Asp
        465                 470                 475

gcc act tgt ttg tta gac tct gga gtt atc cat gta act tgt gct gga     1489
Ala Thr Cys Leu Leu Asp Ser Gly Val Ile His Val Thr Cys Ala Gly
    480                 485                 490

ttt cag aag gag act ttg aca ttt tta aag aaa tca gga cca act ctt     1537
Phe Gln Lys Glu Thr Leu Thr Phe Leu Lys Lys Ser Gly Pro Thr Leu
495                 500                 505                 510

aat gaa gtc att cct gat agt tat aat cga tgt ctt gtt gct ggt ctc     1585
Asn Glu Val Ile Pro Asp Ser Tyr Asn Arg Cys Leu Val Ala Gly Leu
                515                 520                 525

ctc tca cca aga ctt att gat att cag cct tcc agt tta agt caa gaa     1633
Leu Ser Pro Arg Leu Ile Asp Ile Gln Pro Ser Ser Leu Ser Gln Glu
            530                 535                 540

gaa caa tta gaa gct ata ttg tca gca gca att cag aca agt tcc ttg     1681
Glu Gln Leu Glu Ala Ile Leu Ser Ala Ala Ile Gln Thr Ser Ser Leu
        545                 550                 555

gga ctt ttg act ggt tac atc aga aca tgg ata ata gaa gaa caa cca     1729
Gly Leu Leu Thr Gly Tyr Ile Arg Thr Trp Ile Ile Glu Glu Gln Pro
    560                 565                 570

aat tct gct gct aat cta cga ttt gtt ctt gag tgg aca tgg aat aaa     1777
Asn Ser Ala Ala Asn Leu Arg Phe Val Leu Glu Trp Thr Trp Asn Lys
575                 580                 585                 590

gtg gtt ctc aca aaa gaa gag ttt gat agg ctt tgt gtg ccg ctg ttt     1825
Val Val Leu Thr Lys Glu Glu Phe Asp Arg Leu Cys Val Pro Leu Phe
                595                 600                 605
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gac ggt tcg tgt cgt ttt att gac cca cag act att cag tct atc cag     1873
Asp Gly Ser Cys Arg Phe Ile Asp Pro Gln Thr Ile Gln Ser Ile Gln
            610                 615                 620

cag tgc cat tta ctg ctt agc aac ctt agt aca gtc tta agc tgt ttt     1921
Gln Cys His Leu Leu Leu Ser Asn Leu Ser Thr Val Leu Ser Cys Phe
        625                 630                 635

gca atg gag gcc cag ggt atc act gag aga gga ctg gtg gac ttg agc     1969
Ala Met Glu Ala Gln Gly Ile Thr Glu Arg Gly Leu Val Asp Leu Ser
    640                 645                 650

aac aag cac atg gtc acc cag ctt ctc tgt cag tac gca cac atg gtt     2017
Asn Lys His Met Val Thr Gln Leu Leu Cys Gln Tyr Ala His Met Val
655                 660                 665                 670

ctg tgg ttc tgc cac tcg ggg ctt ctg ccc gaa ggc tta gat gat gct     2065
Leu Trp Phe Cys His Ser Gly Leu Leu Pro Glu Gly Leu Asp Asp Ala
                675                 680                 685

ctg cac ctg tca aga cta cgc tac aac tac cct gta att cag aac tac     2113
Leu His Leu Ser Arg Leu Arg Tyr Asn Tyr Pro Val Ile Gln Asn Tyr
            690                 695                 700

tat aca agt cgt cgg cag aag tct gag cgc tca ccc aga ggg aag tgg     2161
Tyr Thr Ser Arg Arg Gln Lys Ser Glu Arg Ser Pro Arg Gly Lys Trp
        705                 710                 715

aac cac gac tgc ttg atg att gat gga tta gtc tct caa cta gga gat     2209
Asn His Asp Cys Leu Met Ile Asp Gly Leu Val Ser Gln Leu Gly Asp
    720                 725                 730

gaa gtt gag aag ttg tgg aag cgg gac gaa ggt ggc aca gga aga tac     2257
Glu Val Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Arg Tyr
735                 740                 745                 750

cct cct gct agc atc cac gca tta ctt gat ata tat tta tta gac aac     2305
Pro Pro Ala Ser Ile His Ala Leu Leu Asp Ile Tyr Leu Leu Asp Asn
                755                 760                 765

att acc gaa gca agc aaa cat gct att acc att tat ttg ctg ctt gat     2353
Ile Thr Glu Ala Ser Lys His Ala Ile Thr Ile Tyr Leu Leu Leu Asp
            770                 775                 780

att atg tat tcc ttt cca aat aaa acg gat acc ccc att gaa tct ttc     2401
Ile Met Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe
        785                 790                 795

ccc act gcc ttt gct att tct tgg ggc caa gtt aag cta gtt caa gga     2449
Pro Thr Ala Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Val Gln Gly
    800                 805                 810

ttt tgg cta cta gat cat aat gac tat gag aat ggt tta gac ctt ctg     2497
Phe Trp Leu Leu Asp His Asn Asp Tyr Glu Asn Gly Leu Asp Leu Leu
815                 820                 825                 830

ttt cac cca gtt act gca aag cct gca tcg tgg caa cat tca aag ata     2545
Phe His Pro Val Thr Ala Lys Pro Ala Ser Trp Gln His Ser Lys Ile
                835                 840                 845

att gaa gct ttt atg agt cag gga gag cac aaa cag gct ctc cgg tat     2593
Ile Glu Ala Phe Met Ser Gln Gly Glu His Lys Gln Ala Leu Arg Tyr
            850                 855                 860

ctt cag aca atg aag cca aca gtg tcc agt agc aat gaa gtt atc ctt     2641
Leu Gln Thr Met Lys Pro Thr Val Ser Ser Ser Asn Glu Val Ile Leu
        865                 870                 875

cac ctc act gtt cta ctt ttt aat aga tgc atg gtt gag gcc tgg aac     2689
His Leu Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn
    880                 885                 890

tta ctg cga cag aat tca aac aga gta aat ata gag gaa tta tta aag     2737
Leu Leu Arg Gln Asn Ser Asn Arg Val Asn Ile Glu Glu Leu Leu Lys
895                 900                 905                 910

cac gct tat gaa gtt tgt cag gag atg ggc tta atg gag gat tta ctg     2785
His Ala Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu
                915                 920                 925
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aag ctg cca ttt aca aac act gag cag gaa tgc tta gtg aaa ttt tta     2833
Lys Leu Pro Phe Thr Asn Thr Glu Gln Glu Cys Leu Val Lys Phe Leu
            930                 935                 940

cag tcc agt acc agt gtt gag aat cat gaa ttc ctt cta gtt cac cat     2881
Gln Ser Ser Thr Ser Val Glu Asn His Glu Phe Leu Leu Val His His
        945                 950                 955

tta cag cgt gcc aat tat att tct gcc ttg aaa cta aac cag att ctg     2929
Leu Gln Arg Ala Asn Tyr Ile Ser Ala Leu Lys Leu Asn Gln Ile Leu
    960                 965                 970

aag aat aat ctc atg agt gat cgt gac cct cga ttg cgg gaa aga tcg     2977
Lys Asn Asn Leu Met Ser Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser
975                 980                 985                 990

gtg act cga aat tct ata tta gac cag tat  ggg aaa atc cta cct  aga   3025
Val Thr Arg Asn Ser Ile Leu Asp Gln Tyr  Gly Lys Ile Leu Pro  Arg
                995                 1000                1005

gtc cag aga aag  tta gct gtt gag cga  gct aag cct tac cac  ctg      3070
Val Gln Arg Lys  Leu Ala Val Glu Arg  Ala Lys Pro Tyr His  Leu
            1010                1015                1020

tcg aca tcc tca  gtt ttt cat gaa gtt  tct aga ccc aaa ccg  tta      3115
Ser Thr Ser Ser  Val Phe His Glu Val  Ser Arg Pro Lys Pro  Leu
            1025                1030                1035

tcg gca ttt cca  aag aaa gct ata act  gga aca gtg tta acc  cga      3160
Ser Ala Phe Pro  Lys Lys Ala Ile Thr  Gly Thr Val Leu Thr  Arg
            1040                1045                1050

tct acg ttc atc  agc aat gtt tta tct  aaa att gga gag gtg  tgg      3205
Ser Thr Phe Ile  Ser Asn Val Leu Ser  Lys Ile Gly Glu Val  Trp
            1055                1060                1065

gca agt cat gag  cct aga aat ggc gtc  tca ctt ttt aac agt  cct      3250
Ala Ser His Glu  Pro Arg Asn Gly Val  Ser Leu Phe Asn Ser  Pro
            1070                1075                1080

aaa aca gaa cag  cca tct cct gta gta  cac tct ttc cca cac  cca      3295
Lys Thr Glu Gln  Pro Ser Pro Val Val  His Ser Phe Pro His  Pro
            1085                1090                1095

gag ctt cct gag  gcg ttt gtt gga act  cca att tca aat aca  tcc      3340
Glu Leu Pro Glu  Ala Phe Val Gly Thr  Pro Ile Ser Asn Thr  Ser
            1100                1105                1110

cag aga att tct  aga tta ctg gat ttg  gtt gtc cat cct gta  ccc      3385
Gln Arg Ile Ser  Arg Leu Leu Asp Leu  Val Val His Pro Val  Pro
            1115                1120                1125

cag cct tct cag  tgt ttg gag ttt att  caa caa agt ccc aca  aga      3430
Gln Pro Ser Gln  Cys Leu Glu Phe Ile  Gln Gln Ser Pro Thr  Arg
            1130                1135                1140

tct cct ttg tgt  ctg ctg tcc agt tcg  tta cca tta agt tca  cag      3475
Ser Pro Leu Cys  Leu Leu Ser Ser Ser  Leu Pro Leu Ser Ser  Gln
            1145                1150                1155

ttt aaa agg cca  cat cag aat acc tcc  agg cct tca gag ttg  ctt      3520
Phe Lys Arg Pro  His Gln Asn Thr Ser  Arg Pro Ser Glu Leu  Leu
            1160                1165                1170

tta ctt gag act  cct ctc ata gtt aag  aaa gct aaa tct ttg  gct      3565
Leu Leu Glu Thr  Pro Leu Ile Val Lys  Lys Ala Lys Ser Leu  Ala
            1175                1180                1185

ctg tca gcc acg  tct tct gga ttt gcc  gag ttt act cct cca  tcc      3610
Leu Ser Ala Thr  Ser Ser Gly Phe Ala  Glu Phe Thr Pro Pro  Ser
            1190                1195                1200

atc ctt agg tct  ggt ttt cga aca aca  cct tta gca tct ccc  tct      3655
Ile Leu Arg Ser  Gly Phe Arg Thr Thr  Pro Leu Ala Ser Pro  Ser
            1205                1210                1215

ttg tca cct gga  aga tct ctc act ccg  cct ttc aga gtt aaa  gaa      3700
Leu Ser Pro Gly  Arg Ser Leu Thr Pro  Pro Phe Arg Val Lys  Glu
            1220                1225                1230
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aca agg att tca  ttc atg gaa gaa ggc  atg aat aca cac tgg  act      3745
Thr Arg Ile Ser  Phe Met Glu Glu Gly  Met Asn Thr His Trp  Thr
            1235                1240                1245

gat aga gct aca  gat gac cga aat aca  aaa gcg ttt gtt agc  aca      3790
Asp Arg Ala Thr  Asp Asp Arg Asn Thr  Lys Ala Phe Val Ser  Thr
            1250                1255                1260

tct ttc cat aaa  tgt gga ctt cca gca  gaa act gag tgg atg  aag      3835
Ser Phe His Lys  Cys Gly Leu Pro Ala  Glu Thr Glu Trp Met  Lys
            1265                1270                1275

acc agt gat aag  aat aca tat ttt cct  ctg gat gtc cct gca  aag      3880
Thr Ser Asp Lys  Asn Thr Tyr Phe Pro  Leu Asp Val Pro Ala  Lys
            1280                1285                1290

ggc cct cag aaa  gtg gtg gca gag tca  ctg gct acc cat tca  gga      3925
Gly Pro Gln Lys  Val Val Ala Glu Ser  Leu Ala Thr His Ser  Gly
            1295                1300                1305

agg ctg gag aaa  ctg gat gtg agc aaa  gaa gac agc aca gct  tcc      3970
Arg Leu Glu Lys  Leu Asp Val Ser Lys  Glu Asp Ser Thr Ala  Ser
            1310                1315                1320

acc agg tca gac  cag acc tcc tta gag  tat cat gac gca cca  tca      4015
Thr Arg Ser Asp  Gln Thr Ser Leu Glu  Tyr His Asp Ala Pro  Ser
            1325                1330                1335

cca gaa gac ttg  gaa ggt gct gtt ttt  gtg tct ccc aag cca  gca      4060
Pro Glu Asp Leu  Glu Gly Ala Val Phe  Val Ser Pro Lys Pro  Ala
            1340                1345                1350

tct tcc tcc act  gaa cta act act aat  tca act cta caa aca  gag      4105
Ser Ser Ser Thr  Glu Leu Thr Thr Asn  Ser Thr Leu Gln Thr  Glu
            1355                1360                1365

agg gat aat gat  aaa gat gcg ttt aag  tca gaa ggt act cct  tca      4150
Arg Asp Asn Asp  Lys Asp Ala Phe Lys  Ser Glu Gly Thr Pro  Ser
            1370                1375                1380

ccc gtg aag aaa  caa ata ggc acg gga  gac gct gca gtg gaa  gca      4195
Pro Val Lys Lys  Gln Ile Gly Thr Gly  Asp Ala Ala Val Glu  Ala
            1385                1390                1395

ttt tca gaa ctg  agt cgc tta gac cct  gtt gaa aga gct gaa  gct      4240
Phe Ser Glu Leu  Ser Arg Leu Asp Pro  Val Glu Arg Ala Glu  Ala
            1400                1405                1410

tct ttt ggt gtg  tcg tca gtc tgt gaa  ggg gaa acc tcc act  tca      4285
Ser Phe Gly Val  Ser Ser Val Cys Glu  Gly Glu Thr Ser Thr  Ser
            1415                1420                1425

aac tcc aag acg  tca gtt ctg gat gga  atc gtg cct att gag  agc      4330
Asn Ser Lys Thr  Ser Val Leu Asp Gly  Ile Val Pro Ile Glu  Ser
            1430                1435                1440

cga acc tcc ata  ctt aca gca gac cac  aaa gag tct gtg gcc  aac      4375
Arg Thr Ser Ile  Leu Thr Ala Asp His  Lys Glu Ser Val Ala  Asn
            1445                1450                1455

acg gtt gca gat  gtt gaa agc tct ggg  tcc acc agc tcc aag  tgc      4420
Thr Val Ala Asp  Val Glu Ser Ser Gly  Ser Thr Ser Ser Lys  Cys
            1460                1465                1470

ccg gtt acc tct  gaa cgc agc ctc ggc  caa aaa cta aca tta  aac      4465
Pro Val Thr Ser  Glu Arg Ser Leu Gly  Gln Lys Leu Thr Leu  Asn
            1475                1480                1485

tta aaa gaa gat  gaa ata gaa gct cat  gta cca aag gag aac  gtt      4510
Leu Lys Glu Asp  Glu Ile Glu Ala His  Val Pro Lys Glu Asn  Val
            1490                1495                1500

ggt tta cca gaa  gaa agc cct cga att  tct gct gct cct tct  gat      4555
Gly Leu Pro Glu  Glu Ser Pro Arg Ile  Ser Ala Ala Pro Ser  Asp
            1505                1510                1515

act cac gag att  cat cta att gga tgt  gaa aat ctt gaa gtt  caa      4600
Thr His Glu Ile  His Leu Ile Gly Cys  Glu Asn Leu Glu Val  Gln
            1520                1525                1530
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aat tca gaa gag  gag gcc aag aat ctt  tca ttt gat gag ttg  tat      4645
Asn Ser Glu Glu  Glu Ala Lys Asn Leu  Ser Phe Asp Glu Leu  Tyr
            1535                1540                1545

ccc tta ggg gca  gag aaa ctt gag tat  aat ctc agt act att  gag      4690
Pro Leu Gly Ala  Glu Lys Leu Glu Tyr  Asn Leu Ser Thr Ile  Glu
            1550                1555                1560

cag cag ttt tgt  gac ttg cct gat gac  aaa gac tct gct gaa  tgt      4735
Gln Gln Phe Cys  Asp Leu Pro Asp Asp  Lys Asp Ser Ala Glu  Cys
            1565                1570                1575

gat gct gct gaa  gta gac ggg gaa ctt  ttt gtg gcc cag agc  aac      4780
Asp Ala Ala Glu  Val Asp Gly Glu Leu  Phe Val Ala Gln Ser  Asn
            1580                1585                1590

ttt acc ctg att  tta gaa ggt gaa gaa  gga gaa gct gag gca  agc      4825
Phe Thr Leu Ile  Leu Glu Gly Glu Glu  Gly Glu Ala Glu Ala  Ser
            1595                1600                1605

gac tct gca gca  cct aat atg tta ccg  aaa tcg acc aag gaa  aaa      4870
Asp Ser Ala Ala  Pro Asn Met Leu Pro  Lys Ser Thr Lys Glu  Lys
            1610                1615                1620

cct gtg tgc tac  agg gaa ccc cat aat  cag gag cgc gtt aca  gat      4915
Pro Val Cys Tyr  Arg Glu Pro His Asn  Gln Glu Arg Val Thr  Asp
            1625                1630                1635

ttg cca tct gct  gtg act gct gac caa  gaa tcc cac aag gta  gag      4960
Leu Pro Ser Ala  Val Thr Ala Asp Gln  Glu Ser His Lys Val  Glu
            1640                1645                1650

act tta ccg tat  gtg cct gaa ccg gtt  aaa gtg gca att gca  gaa      5005
Thr Leu Pro Tyr  Val Pro Glu Pro Val  Lys Val Ala Ile Ala  Glu
            1655                1660                1665

aat ctg ttg gat  gta att aaa gac acc  aga agt aag gaa gca  act      5050
Asn Leu Leu Asp  Val Ile Lys Asp Thr  Arg Ser Lys Glu Ala  Thr
            1670                1675                1680

ccc gtg gca gca  ggt gag gct ggt gat  gag gac gga gca gtg  ata      5095
Pro Val Ala Ala  Gly Glu Ala Gly Asp  Glu Asp Gly Ala Val  Ile
            1685                1690                1695

gtc tca aag gct  gca cat tcg tcc agg  ctg aca aac tct aca  ccg      5140
Val Ser Lys Ala  Ala His Ser Ser Arg  Leu Thr Asn Ser Thr  Pro
            1700                1705                1710

aag act gtt aag  gaa cca cgt gca gag  act gta aat acc agc  cag      5185
Lys Thr Val Lys  Glu Pro Arg Ala Glu  Thr Val Asn Thr Ser  Gln
            1715                1720                1725

agt gat gac atg  gtt tct tct aga act  ctc aca aga agg cag  cat      5230
Ser Asp Asp Met  Val Ser Ser Arg Thr  Leu Thr Arg Arg Gln  His
            1730                1735                1740

gcc cta agc ctg  aat gtc aca tca gaa  caa gag cct tca gca  gtt      5275
Ala Leu Ser Leu  Asn Val Thr Ser Glu  Gln Glu Pro Ser Ala  Val
            1745                1750                1755

gcc act cct aag  aag aga act aga aaa  att aaa gaa act cct  gag      5320
Ala Thr Pro Lys  Lys Arg Thr Arg Lys  Ile Lys Glu Thr Pro  Glu
            1760                1765                1770

tct tct gaa agg  acc tgt tct gac cta  aaa gta gca cct gag  aac      5365
Ser Ser Glu Arg  Thr Cys Ser Asp Leu  Lys Val Ala Pro Glu  Asn
            1775                1780                1785

caa ctg aca gct  cag aat cct ccc gct  cct agg aga aga aag  aag      5410
Gln Leu Thr Ala  Gln Asn Pro Pro Ala  Pro Arg Arg Arg Lys  Lys
            1790                1795                1800

aag gac gtt agc  caa ggc aca ctg cca  agt tct ggt gct gtg  gag      5455
Lys Asp Val Ser  Gln Gly Thr Leu Pro  Ser Ser Gly Ala Val  Glu
            1805                1810                1815

ccg gag ccg gaa  cct cag ggt acg ccg  gga aga ctg agg ctg  aga      5500
Pro Glu Pro Glu  Pro Gln Gly Thr Pro  Gly Arg Leu Arg Leu  Arg
            1820                1825                1830
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acg cag cca ccc  gag cca gca gct gaa  gaa act cct tct aga  aca      5545
Thr Gln Pro Pro  Glu Pro Ala Ala Glu  Glu Thr Pro Ser Arg  Thr
            1835                1840                1845

aaa gtc agg ctt  tca tct gtt aga aag  gga acc cct aga aga  ctt      5590
Lys Val Arg Leu  Ser Ser Val Arg Lys  Gly Thr Pro Arg Arg  Leu
            1850                1855                1860

aag aag tct gta  gaa aat ggg caa agt  ata gaa att cta gat  gat      5635
Lys Lys Ser Val  Glu Asn Gly Gln Ser  Ile Glu Ile Leu Asp  Asp
            1865                1870                1875

ctc aaa ggg agt  gag gca gca agt cat  gac ggg act gtc aca  gag      5680
Leu Lys Gly Ser  Glu Ala Ala Ser His  Asp Gly Thr Val Thr  Glu
            1880                1885                1890

ctg agg aat gcc  aat tta gaa gat act  cag aat atg gag tat  aaa      5725
Leu Arg Asn Ala  Asn Leu Glu Asp Thr  Gln Asn Met Glu Tyr  Lys
            1895                1900                1905

caa gat gaa cac  agt gac cag caa ccg  cct cta aaa cga aag  agg      5770
Gln Asp Glu His  Ser Asp Gln Gln Pro  Pro Leu Lys Arg Lys  Arg
            1910                1915                1920

gtc aga gag aga  gaa gtt agt gtg tca  agt gtg aca gaa gag  cca      5815
Val Arg Glu Arg  Glu Val Ser Val Ser  Ser Val Thr Glu Glu  Pro
            1925                1930                1935

aag ctt gac tca  tcc cag ttg cct ctt  cag aca gga ctc gat  gta      5860
Lys Leu Asp Ser  Ser Gln Leu Pro Leu  Gln Thr Gly Leu Asp  Val
            1940                1945                1950

cct gcc acc cct  agg aaa cgt ggt aga  ccc agg aag gta gtt  ccc      5905
Pro Ala Thr Pro  Arg Lys Arg Gly Arg  Pro Arg Lys Val Val  Pro
            1955                1960                1965

tta gaa gct gac  ggt ggc aca act ggt  aag gaa cag aca agt  cct      5950
Leu Glu Ala Asp  Gly Gly Thr Thr Gly  Lys Glu Gln Thr Ser  Pro
            1970                1975                1980

cag aag aaa gat  gtt ccg gtt gtc cgg  aga tct aca cgg aac  acc      5995
Gln Lys Lys Asp  Val Pro Val Val Arg  Arg Ser Thr Arg Asn  Thr
            1985                1990                1995

cca gct aga aat  gtg agt act tta aaa  aaa tca gtt tta gtg  cca      6040
Pro Ala Arg Asn  Val Ser Thr Leu Lys  Lys Ser Val Leu Val  Pro
            2000                2005                2010

aat aag gaa gct  gct cta gtg gtg aca  tct aag agg aga cct  aca      6085
Asn Lys Glu Ala  Ala Leu Val Val Thr  Ser Lys Arg Arg Pro  Thr
            2015                2020                2025

aag aag tct gca  gag gaa agc tca aaa  gat cca tca gcg gca  gtc      6130
Lys Lys Ser Ala  Glu Glu Ser Ser Lys  Asp Pro Ser Ala Ala  Val
            2030                2035                2040

tca gac tgg gcg  ggt gga gca gcc cac  aca gag tcc gct gac  cga      6175
Ser Asp Trp Ala  Gly Gly Ala Ala His  Thr Glu Ser Ala Asp  Arg
            2045                2050                2055

agg gac gga ctg  ctt gcc gcc gct gct  ctc acg cca tct gcc  cag      6220
Arg Asp Gly Leu  Leu Ala Ala Ala Ala  Leu Thr Pro Ser Ala  Gln
            2060                2065                2070

ggc aca agg act  agg tct aga agg acc  atg ttg ttg acg gac  att      6265
Gly Thr Arg Thr  Arg Ser Arg Arg Thr  Met Leu Leu Thr Asp  Ile
            2075                2080                2085

tct gaa ccc aaa  act gag cct tta ttt  cct cct cct tca gtg  aag      6310
Ser Glu Pro Lys  Thr Glu Pro Leu Phe  Pro Pro Pro Ser Val  Lys
            2090                2095                2100

gtt cca aag aaa  aaa tca aaa gct gag  aac atg gag gcc gca  gcc      6355
Val Pro Lys Lys  Lys Ser Lys Ala Glu  Asn Met Glu Ala Ala  Ala
            2105                2110                2115

cag ctg aaa gaa  ttg gtg tca gat tta  tct tct cag ttt gtt  gtt      6400
Gln Leu Lys Glu  Leu Val Ser Asp Leu  Ser Ser Gln Phe Val  Val
            2120                2125                2130
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tcc cct cct gcc  ttg aga acc agg cag  aaa agt ata tcc aat  act      6445
Ser Pro Pro Ala  Leu Arg Thr Arg Gln  Lys Ser Ile Ser Asn  Thr
            2135                2140                2145

tcc aag ctt cta  ggt gaa ctg gag agt  gac cct aaa cca tta  gag      6490
Ser Lys Leu Leu  Gly Glu Leu Glu Ser  Asp Pro Lys Pro Leu  Glu
            2150                2155                2160

atc ata gaa caa  aaa cca aaa aga agc  agg act gtg aag aca  aga      6535
Ile Ile Glu Gln  Lys Pro Lys Arg Ser  Arg Thr Val Lys Thr  Arg
            2165                2170                2175

gca agc aga aac  aca gga aaa gga agt  tct tgg tca cct cct  cct      6580
Ala Ser Arg Asn  Thr Gly Lys Gly Ser  Ser Trp Ser Pro Pro  Pro
            2180                2185                2190

gta gaa att aag  ctg gtt tct ccc ttg  gcg agt cca gtg gat  gaa      6625
Val Glu Ile Lys  Leu Val Ser Pro Leu  Ala Ser Pro Val Asp  Glu
            2195                2200                2205

ata aag acc ggc  aag cca aga aaa act  gca gaa ata gca gga  aaa      6670
Ile Lys Thr Gly  Lys Pro Arg Lys Thr  Ala Glu Ile Ala Gly  Lys
            2210                2215                2220

act ctt gga agg  ggc aga aag aag cca  tct tct ttt cca aag  caa      6715
Thr Leu Gly Arg  Gly Arg Lys Lys Pro  Ser Ser Phe Pro Lys  Gln
            2225                2230                2235

att tta cgc agg  aaa atg ctg taatttttag cccaagattt taacacgcac      6766
Ile Leu Arg Arg  Lys Met Leu
            2240

ctgtttgtaa aagtcaacag tatttgtgtg gattattaaa gtcaccaatt tggatgaaaa   6826

tactttatat aaattgtaca attttgtaag cagtaaatga gtaactccac atggagtgca   6886

gttcttgtag tgcaggcgtt ttatacgact tgatgcgttt atatcaatgt aaatatgact   6946

tatcattggg aggttaaata aactactgta aagtaaaaaa aaaaaaaaaa aaaaaaaaaa   7006

aaaaaaaaaa aaaaaaaaaa aaaaaaaa                                      7034


<210> SEQ ID NO 12
<211> LENGTH: 2243
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 12

Met Gln Asp Leu Thr Ala Gln Val Thr Ser Asp Leu Leu His Phe Pro
1               5                   10                  15

Glu Val Thr Ile Glu Ala Leu Gly Glu Asp Glu Ile Thr Leu Glu Ser
            20                  25                  30

Val Leu Arg Gly Lys Phe Ala Ala Gly Lys Asn Gly Leu Ala Cys Leu
        35                  40                  45

Ala Cys Gly Pro Gln Leu Glu Val Val Asn Ser Leu Thr Gly Glu Arg
    50                  55                  60

Leu Ser Ala Tyr Arg Phe Ser Gly Val Asn Glu Gln Pro Pro Val Val
65                  70                  75                  80

Leu Ala Val Lys Glu Phe Ser Trp His Lys Arg Thr Gly Leu Leu Ile
                85                  90                  95

Gly Leu Glu Glu Ala Asp Gly Ser Val Leu Cys Leu Tyr Asp Leu Gly
            100                 105                 110

Ile Ser Arg Val Val Lys Ala Val Val Leu Pro Gly Arg Val Thr Ala
        115                 120                 125

Ile Glu Pro Ile Ile Asn His Gly Gly Ala Ser Ala Ser Thr Gln His
    130                 135                 140

Leu His Pro Ser Leu Arg Trp Leu Phe Gly Val Ala Ala Val Val Thr
145                 150                 155                 160
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Asp Val Gly Gln Ile Leu Leu Ile Asp Leu Cys Leu Asp Asp Leu Ser
                165                 170                 175

Cys Ser Gln Asn Glu Val Glu Ala Ser Asp Leu Glu Val Ile Thr Gly
            180                 185                 190

Ile Pro Ala Glu Val Pro His Ile Arg Glu Arg Val Met Arg Glu Gly
        195                 200                 205

Arg His Leu Cys Phe Gln Leu Val Ser Pro Leu Gly Val Ala Ile Ser
    210                 215                 220

Thr Leu Ser Tyr Ile Asn Arg Thr Asn Gln Leu Ala Val Gly Phe Ser
225                 230                 235                 240

Asp Gly Tyr Leu Ala Leu Trp Asn Met Lys Ser Met Lys Arg Glu Tyr
                245                 250                 255

Tyr Thr Gln Leu Glu Gly Gly Arg Val Pro Val His Ala Val Ala Phe
            260                 265                 270

Gln Glu Pro Glu Asn Asp Pro Arg Asn Cys Cys Tyr Leu Trp Ala Val
        275                 280                 285

Gln Ser Thr Gln Asp Ser Glu Gly Asp Val Leu Ser Leu His Leu Leu
    290                 295                 300

Gln Leu Ala Phe Gly Asp Arg Lys Cys Leu Ala Ser Gly Gln Ile Leu
305                 310                 315                 320

Tyr Glu Gly Leu Glu Tyr Cys Glu Glu Arg Tyr Thr Leu Asp Leu Ala
                325                 330                 335

Gly Gly Thr Phe Pro Leu Arg Gly Gln Thr Ser Asn Thr Lys Leu Leu
            340                 345                 350

Gly Cys Gln Ser Ile Glu Arg Phe Pro Ser His Gly Asp Arg Glu Glu
        355                 360                 365

Ser Met Arg Glu Ala Leu Ser Pro Asp Thr Ser Val Ser Val Phe Thr
    370                 375                 380

Trp Gln Val Asn Ile Tyr Gly Gln Gly Lys Pro Ser Val Tyr Leu Gly
385                 390                 395                 400

Leu Phe Asp Ile Asn Arg Trp Tyr His Ala Gln Met Pro Asp Ser Leu
                405                 410                 415

Arg Ser Gly Glu Ser Leu His Asn Cys Ser Tyr Phe Ala Leu Trp Ser
            420                 425                 430

Leu Asp Ser Val Val Ser Arg Thr Ser Pro His His Ile Leu Asp Ile
        435                 440                 445

Leu Val His Glu Arg Ser Leu Asn Arg Gly Val Pro Pro Ser Tyr Pro
    450                 455                 460

Pro Pro Glu Gln Phe Phe Asn Pro Ser Thr Phe Asn Phe Asp Ala Thr
465                 470                 475                 480

Cys Leu Leu Asp Ser Gly Val Ile His Val Thr Cys Ala Gly Phe Gln
                485                 490                 495

Lys Glu Thr Leu Thr Phe Leu Lys Lys Ser Gly Pro Thr Leu Asn Glu
            500                 505                 510

Val Ile Pro Asp Ser Tyr Asn Arg Cys Leu Val Ala Gly Leu Leu Ser
        515                 520                 525

Pro Arg Leu Ile Asp Ile Gln Pro Ser Ser Leu Ser Gln Glu Glu Gln
    530                 535                 540

Leu Glu Ala Ile Leu Ser Ala Ala Ile Gln Thr Ser Ser Leu Gly Leu
545                 550                 555                 560

Leu Thr Gly Tyr Ile Arg Thr Trp Ile Ile Glu Glu Gln Pro Asn Ser
                565                 570                 575

Ala Ala Asn Leu Arg Phe Val Leu Glu Trp Thr Trp Asn Lys Val Val
            580                 585                 590
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Leu Thr Lys Glu Glu Phe Asp Arg Leu Cys Val Pro Leu Phe Asp Gly
        595                 600                 605

Ser Cys Arg Phe Ile Asp Pro Gln Thr Ile Gln Ser Ile Gln Gln Cys
    610                 615                 620

His Leu Leu Leu Ser Asn Leu Ser Thr Val Leu Ser Cys Phe Ala Met
625                 630                 635                 640

Glu Ala Gln Gly Ile Thr Glu Arg Gly Leu Val Asp Leu Ser Asn Lys
                645                 650                 655

His Met Val Thr Gln Leu Leu Cys Gln Tyr Ala His Met Val Leu Trp
            660                 665                 670

Phe Cys His Ser Gly Leu Leu Pro Glu Gly Leu Asp Asp Ala Leu His
        675                 680                 685

Leu Ser Arg Leu Arg Tyr Asn Tyr Pro Val Ile Gln Asn Tyr Tyr Thr
    690                 695                 700

Ser Arg Arg Gln Lys Ser Glu Arg Ser Pro Arg Gly Lys Trp Asn His
705                 710                 715                 720

Asp Cys Leu Met Ile Asp Gly Leu Val Ser Gln Leu Gly Asp Glu Val
                725                 730                 735

Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Arg Tyr Pro Pro
            740                 745                 750

Ala Ser Ile His Ala Leu Leu Asp Ile Tyr Leu Leu Asp Asn Ile Thr
        755                 760                 765

Glu Ala Ser Lys His Ala Ile Thr Ile Tyr Leu Leu Leu Asp Ile Met
    770                 775                 780

Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe Pro Thr
785                 790                 795                 800

Ala Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Val Gln Gly Phe Trp
                805                 810                 815

Leu Leu Asp His Asn Asp Tyr Glu Asn Gly Leu Asp Leu Leu Phe His
            820                 825                 830

Pro Val Thr Ala Lys Pro Ala Ser Trp Gln His Ser Lys Ile Ile Glu
        835                 840                 845

Ala Phe Met Ser Gln Gly Glu His Lys Gln Ala Leu Arg Tyr Leu Gln
    850                 855                 860

Thr Met Lys Pro Thr Val Ser Ser Ser Asn Glu Val Ile Leu His Leu
865                 870                 875                 880

Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn Leu Leu
                885                 890                 895

Arg Gln Asn Ser Asn Arg Val Asn Ile Glu Glu Leu Leu Lys His Ala
            900                 905                 910

Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu Lys Leu
        915                 920                 925

Pro Phe Thr Asn Thr Glu Gln Glu Cys Leu Val Lys Phe Leu Gln Ser
    930                 935                 940

Ser Thr Ser Val Glu Asn His Glu Phe Leu Leu Val His His Leu Gln
945                 950                 955                 960

Arg Ala Asn Tyr Ile Ser Ala Leu Lys Leu Asn Gln Ile Leu Lys Asn
                965                 970                 975

Asn Leu Met Ser Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser Val Thr
            980                 985                 990

Arg Asn Ser Ile Leu Asp Gln Tyr  Gly Lys Ile Leu Pro  Arg Val Gln
        995                 1000                1005

Arg Lys  Leu Ala Val Glu Arg  Ala Lys Pro Tyr His  Leu Ser Thr
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    1010                1015                1020

Ser Ser  Val Phe His Glu Val  Ser Arg Pro Lys Pro  Leu Ser Ala
    1025                1030                1035

Phe Pro  Lys Lys Ala Ile Thr  Gly Thr Val Leu Thr  Arg Ser Thr
    1040                1045                1050

Phe Ile  Ser Asn Val Leu Ser  Lys Ile Gly Glu Val  Trp Ala Ser
    1055                1060                1065

His Glu  Pro Arg Asn Gly Val  Ser Leu Phe Asn Ser  Pro Lys Thr
    1070                1075                1080

Glu Gln  Pro Ser Pro Val Val  His Ser Phe Pro His  Pro Glu Leu
    1085                1090                1095

Pro Glu  Ala Phe Val Gly Thr  Pro Ile Ser Asn Thr  Ser Gln Arg
    1100                1105                1110

Ile Ser  Arg Leu Leu Asp Leu  Val Val His Pro Val  Pro Gln Pro
    1115                1120                1125

Ser Gln  Cys Leu Glu Phe Ile  Gln Gln Ser Pro Thr  Arg Ser Pro
    1130                1135                1140

Leu Cys  Leu Leu Ser Ser Ser  Leu Pro Leu Ser Ser  Gln Phe Lys
    1145                1150                1155

Arg Pro  His Gln Asn Thr Ser  Arg Pro Ser Glu Leu  Leu Leu Leu
    1160                1165                1170

Glu Thr  Pro Leu Ile Val Lys  Lys Ala Lys Ser Leu  Ala Leu Ser
    1175                1180                1185

Ala Thr  Ser Ser Gly Phe Ala  Glu Phe Thr Pro Pro  Ser Ile Leu
    1190                1195                1200

Arg Ser  Gly Phe Arg Thr Thr  Pro Leu Ala Ser Pro  Ser Leu Ser
    1205                1210                1215

Pro Gly  Arg Ser Leu Thr Pro  Pro Phe Arg Val Lys  Glu Thr Arg
    1220                1225                1230

Ile Ser  Phe Met Glu Glu Gly  Met Asn Thr His Trp  Thr Asp Arg
    1235                1240                1245

Ala Thr  Asp Asp Arg Asn Thr  Lys Ala Phe Val Ser  Thr Ser Phe
    1250                1255                1260

His Lys  Cys Gly Leu Pro Ala  Glu Thr Glu Trp Met  Lys Thr Ser
    1265                1270                1275

Asp Lys  Asn Thr Tyr Phe Pro  Leu Asp Val Pro Ala  Lys Gly Pro
    1280                1285                1290

Gln Lys  Val Val Ala Glu Ser  Leu Ala Thr His Ser  Gly Arg Leu
    1295                1300                1305

Glu Lys  Leu Asp Val Ser Lys  Glu Asp Ser Thr Ala  Ser Thr Arg
    1310                1315                1320

Ser Asp  Gln Thr Ser Leu Glu  Tyr His Asp Ala Pro  Ser Pro Glu
    1325                1330                1335

Asp Leu  Glu Gly Ala Val Phe  Val Ser Pro Lys Pro  Ala Ser Ser
    1340                1345                1350

Ser Thr  Glu Leu Thr Thr Asn  Ser Thr Leu Gln Thr  Glu Arg Asp
    1355                1360                1365

Asn Asp  Lys Asp Ala Phe Lys  Ser Glu Gly Thr Pro  Ser Pro Val
    1370                1375                1380

Lys Lys  Gln Ile Gly Thr Gly  Asp Ala Ala Val Glu  Ala Phe Ser
    1385                1390                1395

Glu Leu  Ser Arg Leu Asp Pro  Val Glu Arg Ala Glu  Ala Ser Phe
    1400                1405                1410
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Gly Val  Ser Ser Val Cys Glu  Gly Glu Thr Ser Thr  Ser Asn Ser
    1415                1420                1425

Lys Thr  Ser Val Leu Asp Gly  Ile Val Pro Ile Glu  Ser Arg Thr
    1430                1435                1440

Ser Ile  Leu Thr Ala Asp His  Lys Glu Ser Val Ala  Asn Thr Val
    1445                1450                1455

Ala Asp  Val Glu Ser Ser Gly  Ser Thr Ser Ser Lys  Cys Pro Val
    1460                1465                1470

Thr Ser  Glu Arg Ser Leu Gly  Gln Lys Leu Thr Leu  Asn Leu Lys
    1475                1480                1485

Glu Asp  Glu Ile Glu Ala His  Val Pro Lys Glu Asn  Val Gly Leu
    1490                1495                1500

Pro Glu  Glu Ser Pro Arg Ile  Ser Ala Ala Pro Ser  Asp Thr His
    1505                1510                1515

Glu Ile  His Leu Ile Gly Cys  Glu Asn Leu Glu Val  Gln Asn Ser
    1520                1525                1530

Glu Glu  Glu Ala Lys Asn Leu  Ser Phe Asp Glu Leu  Tyr Pro Leu
    1535                1540                1545

Gly Ala  Glu Lys Leu Glu Tyr  Asn Leu Ser Thr Ile  Glu Gln Gln
    1550                1555                1560

Phe Cys  Asp Leu Pro Asp Asp  Lys Asp Ser Ala Glu  Cys Asp Ala
    1565                1570                1575

Ala Glu  Val Asp Gly Glu Leu  Phe Val Ala Gln Ser  Asn Phe Thr
    1580                1585                1590

Leu Ile  Leu Glu Gly Glu Glu  Gly Glu Ala Glu Ala  Ser Asp Ser
    1595                1600                1605

Ala Ala  Pro Asn Met Leu Pro  Lys Ser Thr Lys Glu  Lys Pro Val
    1610                1615                1620

Cys Tyr  Arg Glu Pro His Asn  Gln Glu Arg Val Thr  Asp Leu Pro
    1625                1630                1635

Ser Ala  Val Thr Ala Asp Gln  Glu Ser His Lys Val  Glu Thr Leu
    1640                1645                1650

Pro Tyr  Val Pro Glu Pro Val  Lys Val Ala Ile Ala  Glu Asn Leu
    1655                1660                1665

Leu Asp  Val Ile Lys Asp Thr  Arg Ser Lys Glu Ala  Thr Pro Val
    1670                1675                1680

Ala Ala  Gly Glu Ala Gly Asp  Glu Asp Gly Ala Val  Ile Val Ser
    1685                1690                1695

Lys Ala  Ala His Ser Ser Arg  Leu Thr Asn Ser Thr  Pro Lys Thr
    1700                1705                1710

Val Lys  Glu Pro Arg Ala Glu  Thr Val Asn Thr Ser  Gln Ser Asp
    1715                1720                1725

Asp Met  Val Ser Ser Arg Thr  Leu Thr Arg Arg Gln  His Ala Leu
    1730                1735                1740

Ser Leu  Asn Val Thr Ser Glu  Gln Glu Pro Ser Ala  Val Ala Thr
    1745                1750                1755

Pro Lys  Lys Arg Thr Arg Lys  Ile Lys Glu Thr Pro  Glu Ser Ser
    1760                1765                1770

Glu Arg  Thr Cys Ser Asp Leu  Lys Val Ala Pro Glu  Asn Gln Leu
    1775                1780                1785

Thr Ala  Gln Asn Pro Pro Ala  Pro Arg Arg Arg Lys  Lys Lys Asp
    1790                1795                1800

Val Ser  Gln Gly Thr Leu Pro  Ser Ser Gly Ala Val  Glu Pro Glu
    1805                1810                1815
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Pro Glu  Pro Gln Gly Thr Pro  Gly Arg Leu Arg Leu  Arg Thr Gln
    1820                1825                1830

Pro Pro  Glu Pro Ala Ala Glu  Glu Thr Pro Ser Arg  Thr Lys Val
    1835                1840                1845

Arg Leu  Ser Ser Val Arg Lys  Gly Thr Pro Arg Arg  Leu Lys Lys
    1850                1855                1860

Ser Val  Glu Asn Gly Gln Ser  Ile Glu Ile Leu Asp  Asp Leu Lys
    1865                1870                1875

Gly Ser  Glu Ala Ala Ser His  Asp Gly Thr Val Thr  Glu Leu Arg
    1880                1885                1890

Asn Ala  Asn Leu Glu Asp Thr  Gln Asn Met Glu Tyr  Lys Gln Asp
    1895                1900                1905

Glu His  Ser Asp Gln Gln Pro  Pro Leu Lys Arg Lys  Arg Val Arg
    1910                1915                1920

Glu Arg  Glu Val Ser Val Ser  Ser Val Thr Glu Glu  Pro Lys Leu
    1925                1930                1935

Asp Ser  Ser Gln Leu Pro Leu  Gln Thr Gly Leu Asp  Val Pro Ala
    1940                1945                1950

Thr Pro  Arg Lys Arg Gly Arg  Pro Arg Lys Val Val  Pro Leu Glu
    1955                1960                1965

Ala Asp  Gly Gly Thr Thr Gly  Lys Glu Gln Thr Ser  Pro Gln Lys
    1970                1975                1980

Lys Asp  Val Pro Val Val Arg  Arg Ser Thr Arg Asn  Thr Pro Ala
    1985                1990                1995

Arg Asn  Val Ser Thr Leu Lys  Lys Ser Val Leu Val  Pro Asn Lys
    2000                2005                2010

Glu Ala  Ala Leu Val Val Thr  Ser Lys Arg Arg Pro  Thr Lys Lys
    2015                2020                2025

Ser Ala  Glu Glu Ser Ser Lys  Asp Pro Ser Ala Ala  Val Ser Asp
    2030                2035                2040

Trp Ala  Gly Gly Ala Ala His  Thr Glu Ser Ala Asp  Arg Arg Asp
    2045                2050                2055

Gly Leu  Leu Ala Ala Ala Ala  Leu Thr Pro Ser Ala  Gln Gly Thr
    2060                2065                2070

Arg Thr  Arg Ser Arg Arg Thr  Met Leu Leu Thr Asp  Ile Ser Glu
    2075                2080                2085

Pro Lys  Thr Glu Pro Leu Phe  Pro Pro Pro Ser Val  Lys Val Pro
    2090                2095                2100

Lys Lys  Lys Ser Lys Ala Glu  Asn Met Glu Ala Ala  Ala Gln Leu
    2105                2110                2115

Lys Glu  Leu Val Ser Asp Leu  Ser Ser Gln Phe Val  Val Ser Pro
    2120                2125                2130

Pro Ala  Leu Arg Thr Arg Gln  Lys Ser Ile Ser Asn  Thr Ser Lys
    2135                2140                2145

Leu Leu  Gly Glu Leu Glu Ser  Asp Pro Lys Pro Leu  Glu Ile Ile
    2150                2155                2160

Glu Gln  Lys Pro Lys Arg Ser  Arg Thr Val Lys Thr  Arg Ala Ser
    2165                2170                2175

Arg Asn  Thr Gly Lys Gly Ser  Ser Trp Ser Pro Pro  Pro Val Glu
    2180                2185                2190

Ile Lys  Leu Val Ser Pro Leu  Ala Ser Pro Val Asp  Glu Ile Lys
    2195                2200                2205

Thr Gly  Lys Pro Arg Lys Thr  Ala Glu Ile Ala Gly  Lys Thr Leu
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    2210                2215                2220

Gly Arg  Gly Arg Lys Lys Pro  Ser Ser Phe Pro Lys  Gln Ile Leu
    2225                2230                2235

Arg Arg  Lys Met Leu
    2240


<210> SEQ ID NO 13
<211> LENGTH: 7215
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (125)..(6922)

<400> SEQUENCE: 13

tgcggctcga gggggccagc gctgacggtg gcgggtacgg caggctcgcg ggcgccgggc     60

ttcgttacat aatctcggac cggaggagcg gtggcacatg gcggcggaac ggcgctgtgg    120

aagt atg cga gac tta aga gct caa gtg act agt ggt ctc ctg cca ttt     169
     Met Arg Asp Leu Arg Ala Gln Val Thr Ser Gly Leu Leu Pro Phe
     1               5                  10                  15

cca gaa gtg act ctt caa gcc ctt gga gaa gac gaa ata aca tta gaa      217
Pro Glu Val Thr Leu Gln Ala Leu Gly Glu Asp Glu Ile Thr Leu Glu
                20                  25                  30

tct gtg ctt cgt gga aag ttt gct gcg ggg aaa aat gga ctt gct tgc      265
Ser Val Leu Arg Gly Lys Phe Ala Ala Gly Lys Asn Gly Leu Ala Cys
            35                  40                  45

ttg gct tgt ggt cca caa ctt gag gta gta aac tct ata aca gga gag      313
Leu Ala Cys Gly Pro Gln Leu Glu Val Val Asn Ser Ile Thr Gly Glu
        50                  55                  60

cga ttg tct gct tac aga ttc agt gga gtc aat gaa cag cct cct gta      361
Arg Leu Ser Ala Tyr Arg Phe Ser Gly Val Asn Glu Gln Pro Pro Val
    65                  70                  75

gtt tta gct gtg aaa gaa ttc tct tgg cag aag aga act gga tta tta      409
Val Leu Ala Val Lys Glu Phe Ser Trp Gln Lys Arg Thr Gly Leu Leu
80                  85                  90                  95

ata gga ttg gaa gaa aca gaa ggg agt gtt ctc tgt ctt tat gac ctt      457
Ile Gly Leu Glu Glu Thr Glu Gly Ser Val Leu Cys Leu Tyr Asp Leu
                100                 105                 110

gga ata tca aaa gta gtt aaa gca gtt gtt ctt cct gga agg gta aca      505
Gly Ile Ser Lys Val Val Lys Ala Val Val Leu Pro Gly Arg Val Thr
            115                 120                 125

gct att gaa cct ata att aat cat gga gga gcc agt gca agc act cag      553
Ala Ile Glu Pro Ile Ile Asn His Gly Gly Ala Ser Ala Ser Thr Gln
        130                 135                 140

cat tta cat cca agt ctg cga tgg ctt ttt gga gtg gca gct gtg gtc      601
His Leu His Pro Ser Leu Arg Trp Leu Phe Gly Val Ala Ala Val Val
    145                 150                 155

act gat gtt gga cag atc ctt ctt att gac cta tgt ttg gat gac ttg      649
Thr Asp Val Gly Gln Ile Leu Leu Ile Asp Leu Cys Leu Asp Asp Leu
160                 165                 170                 175

tca tgc aat caa aat gaa gtt gaa gca tca gat ctt gaa gtt cta act      697
Ser Cys Asn Gln Asn Glu Val Glu Ala Ser Asp Leu Glu Val Leu Thr
                180                 185                 190

ggt atc cca gct gaa gta cca cac att aga gaa agt gtg atg aga gaa      745
Gly Ile Pro Ala Glu Val Pro His Ile Arg Glu Ser Val Met Arg Glu
            195                 200                 205

ggg cgc cat ctg tgt ttc cag tta gta agt cca aca gga aca gcc gtt      793
Gly Arg His Leu Cys Phe Gln Leu Val Ser Pro Thr Gly Thr Ala Val
        210                 215                 220

tca act ctt agt tac ata agc agg aca aat cag ctt gct gca ggt ttt      841
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Ser Thr Leu Ser Tyr Ile Ser Arg Thr Asn Gln Leu Ala Ala Gly Phe
    225                 230                 235

tct gat ggc tat cta gca ctt tgg aac atg aaa agc atg aaa aga gaa      889
Ser Asp Gly Tyr Leu Ala Leu Trp Asn Met Lys Ser Met Lys Arg Glu
240                 245                 250                 255

tat tac ata caa ttg gaa agt gga caa gtt cct gta tat gct gtc act      937
Tyr Tyr Ile Gln Leu Glu Ser Gly Gln Val Pro Val Tyr Ala Val Thr
                260                 265                 270

ttt caa gaa cct gag aat gat cgt cgg aat tgc tgc tac ttg tgg gct      985
Phe Gln Glu Pro Glu Asn Asp Arg Arg Asn Cys Cys Tyr Leu Trp Ala
            275                 280                 285

gtt cag tct aca caa gat agt gaa ggg gat gtt ttg agt ttg cat ctg     1033
Val Gln Ser Thr Gln Asp Ser Glu Gly Asp Val Leu Ser Leu His Leu
        290                 295                 300

ctg cag ctg gcc ttt ggt aat aga aag tgt ttg gca tca gga caa atc     1081
Leu Gln Leu Ala Phe Gly Asn Arg Lys Cys Leu Ala Ser Gly Gln Ile
    305                 310                 315

tta tat gag ggg tta gaa tac tgt gaa gaa aga tac acc ctg gac ctg     1129
Leu Tyr Glu Gly Leu Glu Tyr Cys Glu Glu Arg Tyr Thr Leu Asp Leu
320                 325                 330                 335

aca ggt ggc atg ttc cct ttg agg gga cag acg agt aat acc aaa ttg     1177
Thr Gly Gly Met Phe Pro Leu Arg Gly Gln Thr Ser Asn Thr Lys Leu
                340                 345                 350

ttg gga tgc cag agt ata gag aaa ttt cga tct cat ggt gac agg gag     1225
Leu Gly Cys Gln Ser Ile Glu Lys Phe Arg Ser His Gly Asp Arg Glu
            355                 360                 365

gaa ggc gtg aat gaa gct cta tcg cct gac act agt gtt tca gtc ttt     1273
Glu Gly Val Asn Glu Ala Leu Ser Pro Asp Thr Ser Val Ser Val Phe
        370                 375                 380

acc tgg cag gtg aat ata tat gga cag gga aag cct tct gta tat ttg     1321
Thr Trp Gln Val Asn Ile Tyr Gly Gln Gly Lys Pro Ser Val Tyr Leu
    385                 390                 395

ggg ctt ttt gat ata aat cgt tgg tat cat gca caa atg cca gat tcg     1369
Gly Leu Phe Asp Ile Asn Arg Trp Tyr His Ala Gln Met Pro Asp Ser
400                 405                 410                 415

tta agg tca gga gaa tat cta cat aat tgc tct tat ttt gca ctg tgg     1417
Leu Arg Ser Gly Glu Tyr Leu His Asn Cys Ser Tyr Phe Ala Leu Trp
                420                 425                 430

tca ttg gag tct gtt gta agt agg act tct cca cat ggc atc ttg gat     1465
Ser Leu Glu Ser Val Val Ser Arg Thr Ser Pro His Gly Ile Leu Asp
            435                 440                 445

ata tta gta cat gag aga agt tta aat aga gga gtc cct cct tca tat     1513
Ile Leu Val His Glu Arg Ser Leu Asn Arg Gly Val Pro Pro Ser Tyr
        450                 455                 460

cca cct ccc gag cag ttt ttt aat cca agc act tat aat ttt gat gcc     1561
Pro Pro Pro Glu Gln Phe Phe Asn Pro Ser Thr Tyr Asn Phe Asp Ala
    465                 470                 475

act tgt ttg tta aac tcg gga gtt gtt cat tta act tgt act ggc ttt     1609
Thr Cys Leu Leu Asn Ser Gly Val Val His Leu Thr Cys Thr Gly Phe
480                 485                 490                 495

cag aag gag act ttg act ttt tta aag aaa tca ggt cca tca ctc aat     1657
Gln Lys Glu Thr Leu Thr Phe Leu Lys Lys Ser Gly Pro Ser Leu Asn
                500                 505                 510

gaa ctc att cct gat ggt tat aat cga tgt ctt gta gct ggc ctt ctt     1705
Glu Leu Ile Pro Asp Gly Tyr Asn Arg Cys Leu Val Ala Gly Leu Leu
            515                 520                 525

tcc cca aga ttt gtt gat gtt cag cct tcc agt tta agc caa gaa gaa     1753
Ser Pro Arg Phe Val Asp Val Gln Pro Ser Ser Leu Ser Gln Glu Glu
        530                 535                 540

cag tta gaa gct ata ttg tca gca gca att cag act agt tcc ctg gga     1801
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Gln Leu Glu Ala Ile Leu Ser Ala Ala Ile Gln Thr Ser Ser Leu Gly
    545                 550                 555

ctt ttg act ggt tat atc cga aga tgg ata aca gaa gaa caa cca aat     1849
Leu Leu Thr Gly Tyr Ile Arg Arg Trp Ile Thr Glu Glu Gln Pro Asn
560                 565                 570                 575

tct gcc act aat ttg cgc ttt gtt ctt gaa tgg acg tgg aat aaa gtg     1897
Ser Ala Thr Asn Leu Arg Phe Val Leu Glu Trp Thr Trp Asn Lys Val
                580                 585                 590

gtt ctc aca aaa gag gaa ttt gac aga cta tgt gtg cca tta ttt gat     1945
Val Leu Thr Lys Glu Glu Phe Asp Arg Leu Cys Val Pro Leu Phe Asp
            595                 600                 605

ggt tcg tgt cat ttc atg gat cca caa act ata cag tct atc cag caa     1993
Gly Ser Cys His Phe Met Asp Pro Gln Thr Ile Gln Ser Ile Gln Gln
        610                 615                 620

tgc tat ttg ctt ctt agc aat ctt aat ata gtc ttg agc tgt ttt gca     2041
Cys Tyr Leu Leu Leu Ser Asn Leu Asn Ile Val Leu Ser Cys Phe Ala
    625                 630                 635

tca gaa gcc cga gag atc gct gag aga gga ctg ata gac tta agc aat     2089
Ser Glu Ala Arg Glu Ile Ala Glu Arg Gly Leu Ile Asp Leu Ser Asn
640                 645                 650                 655

aag ttt gtg gtt tcc cac ctc atc tgt cag tat gca caa gtg gtt ctt     2137
Lys Phe Val Val Ser His Leu Ile Cys Gln Tyr Ala Gln Val Val Leu
                660                 665                 670

tgg ttc tct cat tct ggg ctt tta cca gaa ggc ata gat gat tct gtg     2185
Trp Phe Ser His Ser Gly Leu Leu Pro Glu Gly Ile Asp Asp Ser Val
            675                 680                 685

cag ttg tca agg tta tgc tac aac tac cct gta att cag aac tac tac     2233
Gln Leu Ser Arg Leu Cys Tyr Asn Tyr Pro Val Ile Gln Asn Tyr Tyr
        690                 695                 700

acc agt cgt cga cag aag ttt gag cgt tta tca aga ggg aag tgg aat     2281
Thr Ser Arg Arg Gln Lys Phe Glu Arg Leu Ser Arg Gly Lys Trp Asn
    705                 710                 715

ccc gat tgc ttg atg att gat gga ctg gtt tct cag tta gga gag cga     2329
Pro Asp Cys Leu Met Ile Asp Gly Leu Val Ser Gln Leu Gly Glu Arg
720                 725                 730                 735

att gag aag ttg tgg aaa cga gat gaa gga ggc aca gga aaa tat cct     2377
Ile Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Lys Tyr Pro
                740                 745                 750

cct gct agt ctg cat gca gta ctt gat atg tac cta tta gac ggc gtt     2425
Pro Ala Ser Leu His Ala Val Leu Asp Met Tyr Leu Leu Asp Gly Val
            755                 760                 765

act gaa gca gcc aaa cac tct att acc att tat ttg cta ctt gat att     2473
Thr Glu Ala Ala Lys His Ser Ile Thr Ile Tyr Leu Leu Leu Asp Ile
        770                 775                 780

atg tat tcc ttt ccc aac aaa aca gac act ccc att gaa tct ttc cca     2521
Met Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe Pro
    785                 790                 795

act gta ttt gcc att tct tgg ggc caa gtt aaa ctt att cag ggg ttt     2569
Thr Val Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Ile Gln Gly Phe
800                 805                 810                 815

tgg ttg ata gat cat aat gac tat gag agt ggt ttg gat ctt ttg ttt     2617
Trp Leu Ile Asp His Asn Asp Tyr Glu Ser Gly Leu Asp Leu Leu Phe
                820                 825                 830

cat cca gct act gca aaa cct ttg tca tgg caa cat tca aag att att     2665
His Pro Ala Thr Ala Lys Pro Leu Ser Trp Gln His Ser Lys Ile Ile
            835                 840                 845

cag gca ttc atg agt cag ggc gag cac aga caa gcc ctc aga tat att     2713
Gln Ala Phe Met Ser Gln Gly Glu His Arg Gln Ala Leu Arg Tyr Ile
        850                 855                 860

cag aca atg aag cca aca gtg tcc agt ggt aac gat gtt atc ctt cac     2761
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Gln Thr Met Lys Pro Thr Val Ser Ser Gly Asn Asp Val Ile Leu His
    865                 870                 875

ctc act gtt ttg ctt ttt aat agg tgt atg gtt gaa gcc tgg aat ttt     2809
Leu Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn Phe
880                 885                 890                 895

ttg cgg caa cat tgc aat agg ttg aat ata gag gag tta ctg aag cac     2857
Leu Arg Gln His Cys Asn Arg Leu Asn Ile Glu Glu Leu Leu Lys His
                900                 905                 910

atg tat gaa gtc tgt cag gaa atg ggc ttg atg gaa gat tta ctg aag     2905
Met Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu Lys
            915                 920                 925

tta cca ttt aca gac act gag cag gaa tgt tta gtg aaa ttt ttg cag     2953
Leu Pro Phe Thr Asp Thr Glu Gln Glu Cys Leu Val Lys Phe Leu Gln
        930                 935                 940

tcc agt gcc agc gtt cag aat cat gaa ttc ctt tta gtg cac cat ttg     3001
Ser Ser Ala Ser Val Gln Asn His Glu Phe Leu Leu Val His His Leu
    945                 950                 955

cag cgt gcc aat tat gtg cct gcc ttg aag ctg aac caa act ctg aag     3049
Gln Arg Ala Asn Tyr Val Pro Ala Leu Lys Leu Asn Gln Thr Leu Lys
960                 965                 970                 975

att aat gtt atg aat gat cgt gat cct cgt ttg cgg gag aga tca ctg     3097
Ile Asn Val Met Asn Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser Leu
                980                 985                 990

gct cga aat tct ata tta gac cag tat  gga aaa atc ctt cct  aga gtc   3145
Ala Arg Asn Ser Ile Leu Asp Gln Tyr  Gly Lys Ile Leu Pro  Arg Val
            995                 1000                1005

cat cga aaa  tta gcc att gaa cga  gct aag cct tat cat  ctg tca      3190
His Arg Lys  Leu Ala Ile Glu Arg  Ala Lys Pro Tyr His  Leu Ser
        1010                1015                1020

aca tca tca  gtt ttt cga tta gtt  tct aga ccc aaa cca  tta tca      3235
Thr Ser Ser  Val Phe Arg Leu Val  Ser Arg Pro Lys Pro  Leu Ser
        1025                1030                1035

gca gtt cca  aag caa gtt gta aca  gga act gtg ttg aca  aga tct      3280
Ala Val Pro  Lys Gln Val Val Thr  Gly Thr Val Leu Thr  Arg Ser
        1040                1045                1050

gtt ttc atc  aac aat gtg tta tct  aaa att gga gaa gtt  tgg gca      3325
Val Phe Ile  Asn Asn Val Leu Ser  Lys Ile Gly Glu Val  Trp Ala
        1055                1060                1065

agc aaa gaa  cct ata aat agc acc  aca cct ttc aat agt  tct aaa      3370
Ser Lys Glu  Pro Ile Asn Ser Thr  Thr Pro Phe Asn Ser  Ser Lys
        1070                1075                1080

ata gaa gaa  cca tct cct ata gtg  tat tcg ctc cca gct  cca gag      3415
Ile Glu Glu  Pro Ser Pro Ile Val  Tyr Ser Leu Pro Ala  Pro Glu
        1085                1090                1095

ctg cct gag  gca ttt ttt gga aca  cca att tca aaa gca  tca caa      3460
Leu Pro Glu  Ala Phe Phe Gly Thr  Pro Ile Ser Lys Ala  Ser Gln
        1100                1105                1110

aaa att tct  aga ctg cta gat ttg  gtt gtt cag cct gtc  ccc cgg      3505
Lys Ile Ser  Arg Leu Leu Asp Leu  Val Val Gln Pro Val  Pro Arg
        1115                1120                1125

cct tct cag  tgt tcg gag ttt att  cag caa agc tcc atg  aaa tct      3550
Pro Ser Gln  Cys Ser Glu Phe Ile  Gln Gln Ser Ser Met  Lys Ser
        1130                1135                1140

cct ttg tac  cta gta tcc cgt tca  ctg ccc tca agt tcg  caa tta      3595
Pro Leu Tyr  Leu Val Ser Arg Ser  Leu Pro Ser Ser Ser  Gln Leu
        1145                1150                1155

aaa gga tcg  cct cag gcc atc tcc  agg gct tca gaa tta  cat ttg      3640
Lys Gly Ser  Pro Gln Ala Ile Ser  Arg Ala Ser Glu Leu  His Leu
        1160                1165                1170

ctt gaa act  cct ctt gta gtt aag  aaa gct aaa agt ttg  gcc atg      3685
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Leu Glu Thr  Pro Leu Val Val Lys  Lys Ala Lys Ser Leu  Ala Met
        1175                1180                1185

tca gtt act  act tct gga ttt tct  gag ttc act cct cag  tcc atc      3730
Ser Val Thr  Thr Ser Gly Phe Ser  Glu Phe Thr Pro Gln  Ser Ile
        1190                1195                1200

ctg agg tct  act cct cga tca aca  cct tta gca tct ccc  tct cca      3775
Leu Arg Ser  Thr Pro Arg Ser Thr  Pro Leu Ala Ser Pro  Ser Pro
        1205                1210                1215

tca cct gga  agg tct cct caa cga  ctt aaa gaa act aga  att tca      3820
Ser Pro Gly  Arg Ser Pro Gln Arg  Leu Lys Glu Thr Arg  Ile Ser
        1220                1225                1230

ttt gtg gaa  gaa gat gtc cac cca  aaa tgg att cct ggg  gct gca      3865
Phe Val Glu  Glu Asp Val His Pro  Lys Trp Ile Pro Gly  Ala Ala
        1235                1240                1245

gat gat agc  aaa tta gaa gta ttt  act aca cct aaa aaa  tgt gca      3910
Asp Asp Ser  Lys Leu Glu Val Phe  Thr Thr Pro Lys Lys  Cys Ala
        1250                1255                1260

gtt cca gtg  gaa act gaa tgg ccg  aag agc aaa gat agg  acc aca      3955
Val Pro Val  Glu Thr Glu Trp Pro  Lys Ser Lys Asp Arg  Thr Thr
        1265                1270                1275

tct ttt ttc  ctg aac agc cct gaa  aag gag cat caa gaa  atg gat      4000
Ser Phe Phe  Leu Asn Ser Pro Glu  Lys Glu His Gln Glu  Met Asp
        1280                1285                1290

gag ggg tca  caa agt tta gag aaa  ctg gat gtg agc aaa  gga aac      4045
Glu Gly Ser  Gln Ser Leu Glu Lys  Leu Asp Val Ser Lys  Gly Asn
        1295                1300                1305

agc agt gtt  tca atc aca tcc gat  gag act acc tta gag  tat cag      4090
Ser Ser Val  Ser Ile Thr Ser Asp  Glu Thr Thr Leu Glu  Tyr Gln
        1310                1315                1320

gat gca ccg  tca ccg gaa gac ctt  gaa gag act gtt ttc  acg gcc      4135
Asp Ala Pro  Ser Pro Glu Asp Leu  Glu Glu Thr Val Phe  Thr Ala
        1325                1330                1335

tct aag ccc  aaa agc tct tcc act  gca cta act act aat  gta act      4180
Ser Lys Pro  Lys Ser Ser Ser Thr  Ala Leu Thr Thr Asn  Val Thr
        1340                1345                1350

gaa caa act  gaa aag gat gga gat  aaa gat gta ttt gca  tca gaa      4225
Glu Gln Thr  Glu Lys Asp Gly Asp  Lys Asp Val Phe Ala  Ser Glu
        1355                1360                1365

gta act cct  tca gac cta cag aaa  caa atg ggc aat tta  gaa gat      4270
Val Thr Pro  Ser Asp Leu Gln Lys  Gln Met Gly Asn Leu  Glu Asp
        1370                1375                1380

gca gaa aca  aag gat ctc tta gtt  gca gca gag gca ttt  tca gaa      4315
Ala Glu Thr  Lys Asp Leu Leu Val  Ala Ala Glu Ala Phe  Ser Glu
        1385                1390                1395

ttg aat cac  tta agc ccg gtt caa  gga act gaa gct tct  ctt tgt      4360
Leu Asn His  Leu Ser Pro Val Gln  Gly Thr Glu Ala Ser  Leu Cys
        1400                1405                1410

gca cca tca  gtc tat gaa ggg aaa  atc ttc acc cag aag  tcc aag      4405
Ala Pro Ser  Val Tyr Glu Gly Lys  Ile Phe Thr Gln Lys  Ser Lys
        1415                1420                1425

gta cca gtg  ttg gac gaa gga tta  aca tct gtt gaa acc  tac acc      4450
Val Pro Val  Leu Asp Glu Gly Leu  Thr Ser Val Glu Thr  Tyr Thr
        1430                1435                1440

cct gca att  aga gca aat gac aat  aaa tct atg gct gat  gtc ctt      4495
Pro Ala Ile  Arg Ala Asn Asp Asn  Lys Ser Met Ala Asp  Val Leu
        1445                1450                1455

ggt gat ggt  gga aac tcc tcg ctc  act atc tct gaa ggt  cct att      4540
Gly Asp Gly  Gly Asn Ser Ser Leu  Thr Ile Ser Glu Gly  Pro Ile
        1460                1465                1470

gtc tct gag  cgc agg ctt aac cag  gaa gta gcg ctg aac  tta aaa      4585
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Val Ser Glu  Arg Arg Leu Asn Gln  Glu Val Ala Leu Asn  Leu Lys
        1475                1480                1485

gaa gat cat  gaa gta gaa gtt ggt  gta cta aaa gaa agt  gtt gac      4630
Glu Asp His  Glu Val Glu Val Gly  Val Leu Lys Glu Ser  Val Asp
        1490                1495                1500

tta cca gaa  gaa aag ctt cca att  tct gac agc cct cct  gat act      4675
Leu Pro Glu  Glu Lys Leu Pro Ile  Ser Asp Ser Pro Pro  Asp Thr
        1505                1510                1515

caa gaa att  cat gtg att gaa caa  gaa aag ctt gaa gct  caa gat      4720
Gln Glu Ile  His Val Ile Glu Gln  Glu Lys Leu Glu Ala  Gln Asp
        1520                1525                1530

tca gga gaa  gag gct agg aat ctt  tca ttt aat gag tta  tat ccc      4765
Ser Gly Glu  Glu Ala Arg Asn Leu  Ser Phe Asn Glu Leu  Tyr Pro
        1535                1540                1545

tct gga aca  ctt aag ctt cag tac  aat ttt gat act att  gac caa      4810
Ser Gly Thr  Leu Lys Leu Gln Tyr  Asn Phe Asp Thr Ile  Asp Gln
        1550                1555                1560

cag ttt tgt  gac tta gct gat aac  aaa gac act gct gaa  tgt gac      4855
Gln Phe Cys  Asp Leu Ala Asp Asn  Lys Asp Thr Ala Glu  Cys Asp
        1565                1570                1575

att gct gaa  gta gat ggg gaa ctt  ttt gtg gct caa agc  aac ttt      4900
Ile Ala Glu  Val Asp Gly Glu Leu  Phe Val Ala Gln Ser  Asn Phe
        1580                1585                1590

acc ttg ata  ttg gaa ggt gaa gaa  gga gaa gtt gag cca  ggt gat      4945
Thr Leu Ile  Leu Glu Gly Glu Glu  Gly Glu Val Glu Pro  Gly Asp
        1595                1600                1605

ttt gca tca  tct gat gtg tta cct  aaa gca gct aac aca  gca act      4990
Phe Ala Ser  Ser Asp Val Leu Pro  Lys Ala Ala Asn Thr  Ala Thr
        1610                1615                1620

gaa gaa aaa  ctt gta tgc agt ggg  gaa aat gat aat cat  gga caa      5035
Glu Glu Lys  Leu Val Cys Ser Gly  Glu Asn Asp Asn His  Gly Gln
        1625                1630                1635

att gca aat  ttg cca tct gcc gta  act agt gac caa aag  tcc caa      5080
Ile Ala Asn  Leu Pro Ser Ala Val  Thr Ser Asp Gln Lys  Ser Gln
        1640                1645                1650

aaa gta gac  act tta cca tat gtg  cct gaa cct att aaa  gta gca      5125
Lys Val Asp  Thr Leu Pro Tyr Val  Pro Glu Pro Ile Lys  Val Ala
        1655                1660                1665

att gca gaa  aat tta cta gat gta  att aaa gac aca aga  agt aaa      5170
Ile Ala Glu  Asn Leu Leu Asp Val  Ile Lys Asp Thr Arg  Ser Lys
        1670                1675                1680

gaa att act  tca gat aca atg gaa  cag tcc att cat gaa  aca ata      5215
Glu Ile Thr  Ser Asp Thr Met Glu  Gln Ser Ile His Glu  Thr Ile
        1685                1690                1695

cct tta gtg  agc caa aac ata atg  tgt ccc act aaa ttg  gtc aaa      5260
Pro Leu Val  Ser Gln Asn Ile Met  Cys Pro Thr Lys Leu  Val Lys
        1700                1705                1710

tct gca ttt  aag act gct cag gaa  aca agc aca atg act  atg aat      5305
Ser Ala Phe  Lys Thr Ala Gln Glu  Thr Ser Thr Met Thr  Met Asn
        1715                1720                1725

gtc agc cag  gtt gat gac gtg gtt  tcc tcc aaa act cgt  acg aga      5350
Val Ser Gln  Val Asp Asp Val Val  Ser Ser Lys Thr Arg  Thr Arg
        1730                1735                1740

ggt caa cgt  atc caa aac gtg aat  gtc aaa tca gca caa  cag gaa      5395
Gly Gln Arg  Ile Gln Asn Val Asn  Val Lys Ser Ala Gln  Gln Glu
        1745                1750                1755

gca tca gca  gat gtt gct act cct  aag atg cca ggg cag  tca gtc      5440
Ala Ser Ala  Asp Val Ala Thr Pro  Lys Met Pro Gly Gln  Ser Val
        1760                1765                1770

agg aag aaa  act agg aag gca aaa  gaa att tct gaa gct  tct gaa      5485
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Arg Lys Lys  Thr Arg Lys Ala Lys  Glu Ile Ser Glu Ala  Ser Glu
        1775                1780                1785

aac atc tat  tct gat gtc aga gga  cta ttt cag aac cag  caa ata      5530
Asn Ile Tyr  Ser Asp Val Arg Gly  Leu Phe Gln Asn Gln  Gln Ile
        1790                1795                1800

cct caa aat  tct gtt acg cct agg  aga gga agg aga aag  aaa gaa      5575
Pro Gln Asn  Ser Val Thr Pro Arg  Arg Gly Arg Arg Lys  Lys Glu
        1805                1810                1815

gtt aat cag  gac ata cta gaa aac  acc agt tct gtg gaa  caa gaa      5620
Val Asn Gln  Asp Ile Leu Glu Asn  Thr Ser Ser Val Glu  Gln Glu
        1820                1825                1830

tta cag atc  act aca ggt agg gaa  tca aaa aga tta aaa  tca tct      5665
Leu Gln Ile  Thr Thr Gly Arg Glu  Ser Lys Arg Leu Lys  Ser Ser
        1835                1840                1845

cag ctg ttg  gaa cca gca gtt gaa  gaa act act aaa aaa  gaa gtt      5710
Gln Leu Leu  Glu Pro Ala Val Glu  Glu Thr Thr Lys Lys  Glu Val
        1850                1855                1860

aag gtt tca  tct gtt aca aaa agg  act cct aga aga att  aaa aga      5755
Lys Val Ser  Ser Val Thr Lys Arg  Thr Pro Arg Arg Ile  Lys Arg
        1865                1870                1875

tct gta gaa  aat cag gaa agt gtt  gaa att ata aat gat  cta aaa      5800
Ser Val Glu  Asn Gln Glu Ser Val  Glu Ile Ile Asn Asp  Leu Lys
        1880                1885                1890

gtt agt acg  gta aca agt cct agc  aga atg atc aga aaa  ttg aga      5845
Val Ser Thr  Val Thr Ser Pro Ser  Arg Met Ile Arg Lys  Leu Arg
        1895                1900                1905

agt act aat  tta gat gct tct gaa  aat aca gga aat aag  caa gat      5890
Ser Thr Asn  Leu Asp Ala Ser Glu  Asn Thr Gly Asn Lys  Gln Asp
        1910                1915                1920

gat aaa tcc  agt gac aag cag ctg  cgt att aaa cat gtt  aga agg      5935
Asp Lys Ser  Ser Asp Lys Gln Leu  Arg Ile Lys His Val  Arg Arg
        1925                1930                1935

gtc aga ggg  aga gaa gtt agt cca  tca gat gtg aga gaa  gac tcc      5980
Val Arg Gly  Arg Glu Val Ser Pro  Ser Asp Val Arg Glu  Asp Ser
        1940                1945                1950

aac ctt gag  tca tct cag ttg act  gtt caa gca gaa ttt  gat atg      6025
Asn Leu Glu  Ser Ser Gln Leu Thr  Val Gln Ala Glu Phe  Asp Met
        1955                1960                1965

tct gcc ata  cct aga aaa cgt ggt  aga cca aga aaa atc  aat cca      6070
Ser Ala Ile  Pro Arg Lys Arg Gly  Arg Pro Arg Lys Ile  Asn Pro
        1970                1975                1980

tct gaa gat  gta gga tct aag gct  gtt aag gaa gag aga  agc ccc      6115
Ser Glu Asp  Val Gly Ser Lys Ala  Val Lys Glu Glu Arg  Ser Pro
        1985                1990                1995

aag aag aaa  gaa gct ccc agc att  aga agg aga tct aca  aga aat      6160
Lys Lys Lys  Glu Ala Pro Ser Ile  Arg Arg Arg Ser Thr  Arg Asn
        2000                2005                2010

acc cca gct  aaa agt gaa aat gtt  gat gtt gga aaa cca  gct tta      6205
Thr Pro Ala  Lys Ser Glu Asn Val  Asp Val Gly Lys Pro  Ala Leu
        2015                2020                2025

gga aaa tcc  att tta gtg cca aac  gag gaa ctt tcg atg  gtg atg      6250
Gly Lys Ser  Ile Leu Val Pro Asn  Glu Glu Leu Ser Met  Val Met
        2030                2035                2040

agc tct aag  aaa aaa ctt aca aaa  aag act gaa agt caa  agc caa      6295
Ser Ser Lys  Lys Lys Leu Thr Lys  Lys Thr Glu Ser Gln  Ser Gln
        2045                2050                2055

aaa cgt tca  ttg cac tca gta tca  gaa gaa cgc aca gat  gaa atg      6340
Lys Arg Ser  Leu His Ser Val Ser  Glu Glu Arg Thr Asp  Glu Met
        2060                2065                2070

aca cat aaa  gaa aca aat gag cag  gaa gaa aga ttg ctc  gcc aca      6385
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Thr His Lys  Glu Thr Asn Glu Gln  Glu Glu Arg Leu Leu  Ala Thr
        2075                2080                2085

gct tcc ttc  act aaa tca tcc cgc  agc agc agg act cgg  tct agc      6430
Ala Ser Phe  Thr Lys Ser Ser Arg  Ser Ser Arg Thr Arg  Ser Ser
        2090                2095                2100

aag gcc atc  ttg ttg ccg gac ctt  tct gaa cca aac aat  gag cct      6475
Lys Ala Ile  Leu Leu Pro Asp Leu  Ser Glu Pro Asn Asn  Glu Pro
        2105                2110                2115

tta ttt tct  cca gcg tca gaa gtt  cca agg aaa gca aaa  gct aaa      6520
Leu Phe Ser  Pro Ala Ser Glu Val  Pro Arg Lys Ala Lys  Ala Lys
        2120                2125                2130

aaa ata gag  gtt cct gca cag ctg  aaa gaa tta gtt tcg  gat tta      6565
Lys Ile Glu  Val Pro Ala Gln Leu  Lys Glu Leu Val Ser  Asp Leu
        2135                2140                2145

tct tct cag  ttt gtc atc tca cct  cct gct tta agg agc  aga caa      6610
Ser Ser Gln  Phe Val Ile Ser Pro  Pro Ala Leu Arg Ser  Arg Gln
        2150                2155                2160

aaa aac aca  tcc aat aag aac aag  ctt gaa gat gaa ctg  aaa gat      6655
Lys Asn Thr  Ser Asn Lys Asn Lys  Leu Glu Asp Glu Leu  Lys Asp
        2165                2170                2175

gat gca caa  tca gta gaa act ctg  gga aag cca aaa gcg  aaa cga      6700
Asp Ala Gln  Ser Val Glu Thr Leu  Gly Lys Pro Lys Ala  Lys Arg
        2180                2185                2190

atc agg acg  tca aaa aca aaa caa  gca agc aaa aac aca  gaa aaa      6745
Ile Arg Thr  Ser Lys Thr Lys Gln  Ala Ser Lys Asn Thr  Glu Lys
        2195                2200                2205

gaa agt gct  tgg tca ctt cct ccc  ata gaa att cgg ctg  att tcc      6790
Glu Ser Ala  Trp Ser Leu Pro Pro  Ile Glu Ile Arg Leu  Ile Ser
        2210                2215                2220

ccc ttg gct  agc cca gct gac gga  gtc aag agc aaa cca  aga aaa      6835
Pro Leu Ala  Ser Pro Ala Asp Gly  Val Lys Ser Lys Pro  Arg Lys
        2225                2230                2235

act aca gaa  gtg aca gga aca ggt  ctt gga agg aac aga  aag aaa      6880
Thr Thr Glu  Val Thr Gly Thr Gly  Leu Gly Arg Asn Arg  Lys Lys
        2240                2245                2250

ctg tct tcc  tat cca aag caa att  tta cgc aga aaa atg  ctg          6922
Leu Ser Ser  Tyr Pro Lys Gln Ile  Leu Arg Arg Lys Met  Leu
        2255                2260                2265

taatttcttg ggaagatttt aatgtacacc tatttgtaaa gtcatcagaa tagtgtggat   6982

tattaaatat ctagtttgga agaaaataat ttatataaat tattgtaaat ttttatgtaa   7042

acagaaggtc ttcaataagt aaagtaactc catatggagt gattgtttca gtccaggcaa   7102

tttttctatt ttatattaag acttcataca tttatatatg taaatatggc ttattaatgg   7162

aatgttaaat aaaatgtata cttctcaaaa aaaaaaaaaa aaaaaaaaaa aaa          7215


<210> SEQ ID NO 14
<211> LENGTH: 2266
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Arg Asp Leu Arg Ala Gln Val Thr Ser Gly Leu Leu Pro Phe Pro
1               5                  10                  15

Glu Val Thr Leu Gln Ala Leu Gly Glu Asp Glu Ile Thr Leu Glu Ser
            20                  25                  30

Val Leu Arg Gly Lys Phe Ala Ala Gly Lys Asn Gly Leu Ala Cys Leu
        35                  40                  45

Ala Cys Gly Pro Gln Leu Glu Val Val Asn Ser Ile Thr Gly Glu Arg
    50                  55                  60
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Leu Ser Ala Tyr Arg Phe Ser Gly Val Asn Glu Gln Pro Pro Val Val
65                  70                  75                  80

Leu Ala Val Lys Glu Phe Ser Trp Gln Lys Arg Thr Gly Leu Leu Ile
                85                  90                  95

Gly Leu Glu Glu Thr Glu Gly Ser Val Leu Cys Leu Tyr Asp Leu Gly
            100                 105                 110

Ile Ser Lys Val Val Lys Ala Val Val Leu Pro Gly Arg Val Thr Ala
        115                 120                 125

Ile Glu Pro Ile Ile Asn His Gly Gly Ala Ser Ala Ser Thr Gln His
    130                 135                 140

Leu His Pro Ser Leu Arg Trp Leu Phe Gly Val Ala Ala Val Val Thr
145                 150                 155                 160

Asp Val Gly Gln Ile Leu Leu Ile Asp Leu Cys Leu Asp Asp Leu Ser
                165                 170                 175

Cys Asn Gln Asn Glu Val Glu Ala Ser Asp Leu Glu Val Leu Thr Gly
            180                 185                 190

Ile Pro Ala Glu Val Pro His Ile Arg Glu Ser Val Met Arg Glu Gly
        195                 200                 205

Arg His Leu Cys Phe Gln Leu Val Ser Pro Thr Gly Thr Ala Val Ser
    210                 215                 220

Thr Leu Ser Tyr Ile Ser Arg Thr Asn Gln Leu Ala Ala Gly Phe Ser
225                 230                 235                 240

Asp Gly Tyr Leu Ala Leu Trp Asn Met Lys Ser Met Lys Arg Glu Tyr
                245                 250                 255

Tyr Ile Gln Leu Glu Ser Gly Gln Val Pro Val Tyr Ala Val Thr Phe
            260                 265                 270

Gln Glu Pro Glu Asn Asp Arg Arg Asn Cys Cys Tyr Leu Trp Ala Val
        275                 280                 285

Gln Ser Thr Gln Asp Ser Glu Gly Asp Val Leu Ser Leu His Leu Leu
    290                 295                 300

Gln Leu Ala Phe Gly Asn Arg Lys Cys Leu Ala Ser Gly Gln Ile Leu
305                 310                 315                 320

Tyr Glu Gly Leu Glu Tyr Cys Glu Glu Arg Tyr Thr Leu Asp Leu Thr
                325                 330                 335

Gly Gly Met Phe Pro Leu Arg Gly Gln Thr Ser Asn Thr Lys Leu Leu
            340                 345                 350

Gly Cys Gln Ser Ile Glu Lys Phe Arg Ser His Gly Asp Arg Glu Glu
        355                 360                 365

Gly Val Asn Glu Ala Leu Ser Pro Asp Thr Ser Val Ser Val Phe Thr
    370                 375                 380

Trp Gln Val Asn Ile Tyr Gly Gln Gly Lys Pro Ser Val Tyr Leu Gly
385                 390                 395                 400

Leu Phe Asp Ile Asn Arg Trp Tyr His Ala Gln Met Pro Asp Ser Leu
                405                 410                 415

Arg Ser Gly Glu Tyr Leu His Asn Cys Ser Tyr Phe Ala Leu Trp Ser
            420                 425                 430

Leu Glu Ser Val Val Ser Arg Thr Ser Pro His Gly Ile Leu Asp Ile
        435                 440                 445

Leu Val His Glu Arg Ser Leu Asn Arg Gly Val Pro Pro Ser Tyr Pro
    450                 455                 460

Pro Pro Glu Gln Phe Phe Asn Pro Ser Thr Tyr Asn Phe Asp Ala Thr
465                 470                 475                 480

Cys Leu Leu Asn Ser Gly Val Val His Leu Thr Cys Thr Gly Phe Gln
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                485                 490                 495

Lys Glu Thr Leu Thr Phe Leu Lys Lys Ser Gly Pro Ser Leu Asn Glu
            500                 505                 510

Leu Ile Pro Asp Gly Tyr Asn Arg Cys Leu Val Ala Gly Leu Leu Ser
        515                 520                 525

Pro Arg Phe Val Asp Val Gln Pro Ser Ser Leu Ser Gln Glu Glu Gln
    530                 535                 540

Leu Glu Ala Ile Leu Ser Ala Ala Ile Gln Thr Ser Ser Leu Gly Leu
545                 550                 555                 560

Leu Thr Gly Tyr Ile Arg Arg Trp Ile Thr Glu Glu Gln Pro Asn Ser
                565                 570                 575

Ala Thr Asn Leu Arg Phe Val Leu Glu Trp Thr Trp Asn Lys Val Val
            580                 585                 590

Leu Thr Lys Glu Glu Phe Asp Arg Leu Cys Val Pro Leu Phe Asp Gly
        595                 600                 605

Ser Cys His Phe Met Asp Pro Gln Thr Ile Gln Ser Ile Gln Gln Cys
    610                 615                 620

Tyr Leu Leu Leu Ser Asn Leu Asn Ile Val Leu Ser Cys Phe Ala Ser
625                 630                 635                 640

Glu Ala Arg Glu Ile Ala Glu Arg Gly Leu Ile Asp Leu Ser Asn Lys
                645                 650                 655

Phe Val Val Ser His Leu Ile Cys Gln Tyr Ala Gln Val Val Leu Trp
            660                 665                 670

Phe Ser His Ser Gly Leu Leu Pro Glu Gly Ile Asp Asp Ser Val Gln
        675                 680                 685

Leu Ser Arg Leu Cys Tyr Asn Tyr Pro Val Ile Gln Asn Tyr Tyr Thr
    690                 695                 700

Ser Arg Arg Gln Lys Phe Glu Arg Leu Ser Arg Gly Lys Trp Asn Pro
705                 710                 715                 720

Asp Cys Leu Met Ile Asp Gly Leu Val Ser Gln Leu Gly Glu Arg Ile
                725                 730                 735

Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Lys Tyr Pro Pro
            740                 745                 750

Ala Ser Leu His Ala Val Leu Asp Met Tyr Leu Leu Asp Gly Val Thr
        755                 760                 765

Glu Ala Ala Lys His Ser Ile Thr Ile Tyr Leu Leu Leu Asp Ile Met
    770                 775                 780

Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser Phe Pro Thr
785                 790                 795                 800

Val Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Ile Gln Gly Phe Trp
                805                 810                 815

Leu Ile Asp His Asn Asp Tyr Glu Ser Gly Leu Asp Leu Leu Phe His
            820                 825                 830

Pro Ala Thr Ala Lys Pro Leu Ser Trp Gln His Ser Lys Ile Ile Gln
        835                 840                 845

Ala Phe Met Ser Gln Gly Glu His Arg Gln Ala Leu Arg Tyr Ile Gln
    850                 855                 860

Thr Met Lys Pro Thr Val Ser Ser Gly Asn Asp Val Ile Leu His Leu
865                 870                 875                 880

Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp Asn Phe Leu
                885                 890                 895

Arg Gln His Cys Asn Arg Leu Asn Ile Glu Glu Leu Leu Lys His Met
            900                 905                 910
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Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu Leu Lys Leu
        915                 920                 925

Pro Phe Thr Asp Thr Glu Gln Glu Cys Leu Val Lys Phe Leu Gln Ser
    930                 935                 940

Ser Ala Ser Val Gln Asn His Glu Phe Leu Leu Val His His Leu Gln
945                 950                 955                 960

Arg Ala Asn Tyr Val Pro Ala Leu Lys Leu Asn Gln Thr Leu Lys Ile
                965                 970                 975

Asn Val Met Asn Asp Arg Asp Pro Arg Leu Arg Glu Arg Ser Leu Ala
            980                 985                 990

Arg Asn Ser Ile Leu Asp Gln Tyr  Gly Lys Ile Leu Pro  Arg Val His
        995                 1000                1005

Arg Lys  Leu Ala Ile Glu Arg  Ala Lys Pro Tyr His  Leu Ser Thr
    1010                1015                1020

Ser Ser  Val Phe Arg Leu Val  Ser Arg Pro Lys Pro  Leu Ser Ala
    1025                1030                1035

Val Pro  Lys Gln Val Val Thr  Gly Thr Val Leu Thr  Arg Ser Val
    1040                1045                1050

Phe Ile  Asn Asn Val Leu Ser  Lys Ile Gly Glu Val  Trp Ala Ser
    1055                1060                1065

Lys Glu  Pro Ile Asn Ser Thr  Thr Pro Phe Asn Ser  Ser Lys Ile
    1070                1075                1080

Glu Glu  Pro Ser Pro Ile Val  Tyr Ser Leu Pro Ala  Pro Glu Leu
    1085                1090                1095

Pro Glu  Ala Phe Phe Gly Thr  Pro Ile Ser Lys Ala  Ser Gln Lys
    1100                1105                1110

Ile Ser  Arg Leu Leu Asp Leu  Val Val Gln Pro Val  Pro Arg Pro
    1115                1120                1125

Ser Gln  Cys Ser Glu Phe Ile  Gln Gln Ser Ser Met  Lys Ser Pro
    1130                1135                1140

Leu Tyr  Leu Val Ser Arg Ser  Leu Pro Ser Ser Ser  Gln Leu Lys
    1145                1150                1155

Gly Ser  Pro Gln Ala Ile Ser  Arg Ala Ser Glu Leu  His Leu Leu
    1160                1165                1170

Glu Thr  Pro Leu Val Val Lys  Lys Ala Lys Ser Leu  Ala Met Ser
    1175                1180                1185

Val Thr  Thr Ser Gly Phe Ser  Glu Phe Thr Pro Gln  Ser Ile Leu
    1190                1195                1200

Arg Ser  Thr Pro Arg Ser Thr  Pro Leu Ala Ser Pro  Ser Pro Ser
    1205                1210                1215

Pro Gly  Arg Ser Pro Gln Arg  Leu Lys Glu Thr Arg  Ile Ser Phe
    1220                1225                1230

Val Glu  Glu Asp Val His Pro  Lys Trp Ile Pro Gly  Ala Ala Asp
    1235                1240                1245

Asp Ser  Lys Leu Glu Val Phe  Thr Thr Pro Lys Lys  Cys Ala Val
    1250                1255                1260

Pro Val  Glu Thr Glu Trp Pro  Lys Ser Lys Asp Arg  Thr Thr Ser
    1265                1270                1275

Phe Phe  Leu Asn Ser Pro Glu  Lys Glu His Gln Glu  Met Asp Glu
    1280                1285                1290

Gly Ser  Gln Ser Leu Glu Lys  Leu Asp Val Ser Lys  Gly Asn Ser
    1295                1300                1305

Ser Val  Ser Ile Thr Ser Asp  Glu Thr Thr Leu Glu  Tyr Gln Asp
    1310                1315                1320
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Ala Pro  Ser Pro Glu Asp Leu  Glu Glu Thr Val Phe  Thr Ala Ser
    1325                1330                1335

Lys Pro  Lys Ser Ser Ser Thr  Ala Leu Thr Thr Asn  Val Thr Glu
    1340                1345                1350

Gln Thr  Glu Lys Asp Gly Asp  Lys Asp Val Phe Ala  Ser Glu Val
    1355                1360                1365

Thr Pro  Ser Asp Leu Gln Lys  Gln Met Gly Asn Leu  Glu Asp Ala
    1370                1375                1380

Glu Thr  Lys Asp Leu Leu Val  Ala Ala Glu Ala Phe  Ser Glu Leu
    1385                1390                1395

Asn His  Leu Ser Pro Val Gln  Gly Thr Glu Ala Ser  Leu Cys Ala
    1400                1405                1410

Pro Ser  Val Tyr Glu Gly Lys  Ile Phe Thr Gln Lys  Ser Lys Val
    1415                1420                1425

Pro Val  Leu Asp Glu Gly Leu  Thr Ser Val Glu Thr  Tyr Thr Pro
    1430                1435                1440

Ala Ile  Arg Ala Asn Asp Asn  Lys Ser Met Ala Asp  Val Leu Gly
    1445                1450                1455

Asp Gly  Gly Asn Ser Ser Leu  Thr Ile Ser Glu Gly  Pro Ile Val
    1460                1465                1470

Ser Glu  Arg Arg Leu Asn Gln  Glu Val Ala Leu Asn  Leu Lys Glu
    1475                1480                1485

Asp His  Glu Val Glu Val Gly  Val Leu Lys Glu Ser  Val Asp Leu
    1490                1495                1500

Pro Glu  Glu Lys Leu Pro Ile  Ser Asp Ser Pro Pro  Asp Thr Gln
    1505                1510                1515

Glu Ile  His Val Ile Glu Gln  Glu Lys Leu Glu Ala  Gln Asp Ser
    1520                1525                1530

Gly Glu  Glu Ala Arg Asn Leu  Ser Phe Asn Glu Leu  Tyr Pro Ser
    1535                1540                1545

Gly Thr  Leu Lys Leu Gln Tyr  Asn Phe Asp Thr Ile  Asp Gln Gln
    1550                1555                1560

Phe Cys  Asp Leu Ala Asp Asn  Lys Asp Thr Ala Glu  Cys Asp Ile
    1565                1570                1575

Ala Glu  Val Asp Gly Glu Leu  Phe Val Ala Gln Ser  Asn Phe Thr
    1580                1585                1590

Leu Ile  Leu Glu Gly Glu Glu  Gly Glu Val Glu Pro  Gly Asp Phe
    1595                1600                1605

Ala Ser  Ser Asp Val Leu Pro  Lys Ala Ala Asn Thr  Ala Thr Glu
    1610                1615                1620

Glu Lys  Leu Val Cys Ser Gly  Glu Asn Asp Asn His  Gly Gln Ile
    1625                1630                1635

Ala Asn  Leu Pro Ser Ala Val  Thr Ser Asp Gln Lys  Ser Gln Lys
    1640                1645                1650

Val Asp  Thr Leu Pro Tyr Val  Pro Glu Pro Ile Lys  Val Ala Ile
    1655                1660                1665

Ala Glu  Asn Leu Leu Asp Val  Ile Lys Asp Thr Arg  Ser Lys Glu
    1670                1675                1680

Ile Thr  Ser Asp Thr Met Glu  Gln Ser Ile His Glu  Thr Ile Pro
    1685                1690                1695

Leu Val  Ser Gln Asn Ile Met  Cys Pro Thr Lys Leu  Val Lys Ser
    1700                1705                1710

Ala Phe  Lys Thr Ala Gln Glu  Thr Ser Thr Met Thr  Met Asn Val
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    1715                1720                1725

Ser Gln  Val Asp Asp Val Val  Ser Ser Lys Thr Arg  Thr Arg Gly
    1730                1735                1740

Gln Arg  Ile Gln Asn Val Asn  Val Lys Ser Ala Gln  Gln Glu Ala
    1745                1750                1755

Ser Ala  Asp Val Ala Thr Pro  Lys Met Pro Gly Gln  Ser Val Arg
    1760                1765                1770

Lys Lys  Thr Arg Lys Ala Lys  Glu Ile Ser Glu Ala  Ser Glu Asn
    1775                1780                1785

Ile Tyr  Ser Asp Val Arg Gly  Leu Phe Gln Asn Gln  Gln Ile Pro
    1790                1795                1800

Gln Asn  Ser Val Thr Pro Arg  Arg Gly Arg Arg Lys  Lys Glu Val
    1805                1810                1815

Asn Gln  Asp Ile Leu Glu Asn  Thr Ser Ser Val Glu  Gln Glu Leu
    1820                1825                1830

Gln Ile  Thr Thr Gly Arg Glu  Ser Lys Arg Leu Lys  Ser Ser Gln
    1835                1840                1845

Leu Leu  Glu Pro Ala Val Glu  Glu Thr Thr Lys Lys  Glu Val Lys
    1850                1855                1860

Val Ser  Ser Val Thr Lys Arg  Thr Pro Arg Arg Ile  Lys Arg Ser
    1865                1870                1875

Val Glu  Asn Gln Glu Ser Val  Glu Ile Ile Asn Asp  Leu Lys Val
    1880                1885                1890

Ser Thr  Val Thr Ser Pro Ser  Arg Met Ile Arg Lys  Leu Arg Ser
    1895                1900                1905

Thr Asn  Leu Asp Ala Ser Glu  Asn Thr Gly Asn Lys  Gln Asp Asp
    1910                1915                1920

Lys Ser  Ser Asp Lys Gln Leu  Arg Ile Lys His Val  Arg Arg Val
    1925                1930                1935

Arg Gly  Arg Glu Val Ser Pro  Ser Asp Val Arg Glu  Asp Ser Asn
    1940                1945                1950

Leu Glu  Ser Ser Gln Leu Thr  Val Gln Ala Glu Phe  Asp Met Ser
    1955                1960                1965

Ala Ile  Pro Arg Lys Arg Gly  Arg Pro Arg Lys Ile  Asn Pro Ser
    1970                1975                1980

Glu Asp  Val Gly Ser Lys Ala  Val Lys Glu Glu Arg  Ser Pro Lys
    1985                1990                1995

Lys Lys  Glu Ala Pro Ser Ile  Arg Arg Arg Ser Thr  Arg Asn Thr
    2000                2005                2010

Pro Ala  Lys Ser Glu Asn Val  Asp Val Gly Lys Pro  Ala Leu Gly
    2015                2020                2025

Lys Ser  Ile Leu Val Pro Asn  Glu Glu Leu Ser Met  Val Met Ser
    2030                2035                2040

Ser Lys  Lys Lys Leu Thr Lys  Lys Thr Glu Ser Gln  Ser Gln Lys
    2045                2050                2055

Arg Ser  Leu His Ser Val Ser  Glu Glu Arg Thr Asp  Glu Met Thr
    2060                2065                2070

His Lys  Glu Thr Asn Glu Gln  Glu Glu Arg Leu Leu  Ala Thr Ala
    2075                2080                2085

Ser Phe  Thr Lys Ser Ser Arg  Ser Ser Arg Thr Arg  Ser Ser Lys
    2090                2095                2100

Ala Ile  Leu Leu Pro Asp Leu  Ser Glu Pro Asn Asn  Glu Pro Leu
    2105                2110                2115
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Phe Ser  Pro Ala Ser Glu Val  Pro Arg Lys Ala Lys  Ala Lys Lys
    2120                2125                2130

Ile Glu  Val Pro Ala Gln Leu  Lys Glu Leu Val Ser  Asp Leu Ser
    2135                2140                2145

Ser Gln  Phe Val Ile Ser Pro  Pro Ala Leu Arg Ser  Arg Gln Lys
    2150                2155                2160

Asn Thr  Ser Asn Lys Asn Lys  Leu Glu Asp Glu Leu  Lys Asp Asp
    2165                2170                2175

Ala Gln  Ser Val Glu Thr Leu  Gly Lys Pro Lys Ala  Lys Arg Ile
    2180                2185                2190

Arg Thr  Ser Lys Thr Lys Gln  Ala Ser Lys Asn Thr  Glu Lys Glu
    2195                2200                2205

Ser Ala  Trp Ser Leu Pro Pro  Ile Glu Ile Arg Leu  Ile Ser Pro
    2210                2215                2220

Leu Ala  Ser Pro Ala Asp Gly  Val Lys Ser Lys Pro  Arg Lys Thr
    2225                2230                2235

Thr Glu  Val Thr Gly Thr Gly  Leu Gly Arg Asn Arg  Lys Lys Leu
    2240                2245                2250

Ser Ser  Tyr Pro Lys Gln Ile  Leu Arg Arg Lys Met  Leu
    2255                2260                2265


<210> SEQ ID NO 15
<211> LENGTH: 7215
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (98)..(6922)

<400> SEQUENCE: 15

tgcggctcga gggggccagc gctgacggtg gcgggtacgg caggctcgcg ggcgccgggc     60

ttcgttacat aatctcggac cggaggagcg gtggcac atg gcg gcg gaa cgg cgc     115
                                        Met Ala Ala Glu Arg Arg
                                        1               5

tgt gga agt atg cga gac tta aga gct caa gtg act agt ggt ctc ctg      163
Cys Gly Ser Met Arg Asp Leu Arg Ala Gln Val Thr Ser Gly Leu Leu
            10                  15                  20

cca ttt cca gaa gtg act ctt caa gcc ctt gga gaa gac gaa ata aca      211
Pro Phe Pro Glu Val Thr Leu Gln Ala Leu Gly Glu Asp Glu Ile Thr
        25                  30                  35

tta gaa tct gtg ctt cgt gga aag ttt gct gcg ggg aaa aat gga ctt      259
Leu Glu Ser Val Leu Arg Gly Lys Phe Ala Ala Gly Lys Asn Gly Leu
    40                  45                  50

gct tgc ttg gct tgt ggt cca caa ctt gag gta gta aac tct ata aca      307
Ala Cys Leu Ala Cys Gly Pro Gln Leu Glu Val Val Asn Ser Ile Thr
55                  60                  65                  70

gga gag cga ttg tct gct tac aga ttc agt gga gtc aat gaa cag cct      355
Gly Glu Arg Leu Ser Ala Tyr Arg Phe Ser Gly Val Asn Glu Gln Pro
                75                  80                  85

cct gta gtt tta gct gtg aaa gaa ttc tct tgg cag aag aga act gga      403
Pro Val Val Leu Ala Val Lys Glu Phe Ser Trp Gln Lys Arg Thr Gly
            90                  95                  100

tta tta ata gga ttg gaa gaa aca gaa ggg agt gtt ctc tgt ctt tat      451
Leu Leu Ile Gly Leu Glu Glu Thr Glu Gly Ser Val Leu Cys Leu Tyr
        105                 110                 115

gac ctt gga ata tca aaa gta gtt aaa gca gtt gtt ctt cct gga agg      499
Asp Leu Gly Ile Ser Lys Val Val Lys Ala Val Val Leu Pro Gly Arg
    120                 125                 130

gta aca gct att gaa cct ata att aat cat gga gga gcc agt gca agc      547
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Val Thr Ala Ile Glu Pro Ile Ile Asn His Gly Gly Ala Ser Ala Ser
135                 140                 145                 150

act cag cat tta cat cca agt ctg cga tgg ctt ttt gga gtg gca gct      595
Thr Gln His Leu His Pro Ser Leu Arg Trp Leu Phe Gly Val Ala Ala
                155                 160                 165

gtg gtc act gat gtt gga cag atc ctt ctt att gac cta tgt ttg gat      643
Val Val Thr Asp Val Gly Gln Ile Leu Leu Ile Asp Leu Cys Leu Asp
            170                 175                 180

gac ttg tca tgc aat caa aat gaa gtt gaa gca tca gat ctt gaa gtt      691
Asp Leu Ser Cys Asn Gln Asn Glu Val Glu Ala Ser Asp Leu Glu Val
        185                 190                 195

cta act ggt atc cca gct gaa gta cca cac att aga gaa agt gtg atg      739
Leu Thr Gly Ile Pro Ala Glu Val Pro His Ile Arg Glu Ser Val Met
    200                 205                 210

aga gaa ggg cgc cat ctg tgt ttc cag tta gta agt cca aca gga aca      787
Arg Glu Gly Arg His Leu Cys Phe Gln Leu Val Ser Pro Thr Gly Thr
215                 220                 225                 230

gcc gtt tca act ctt agt tac ata agc agg aca aat cag ctt gct gca      835
Ala Val Ser Thr Leu Ser Tyr Ile Ser Arg Thr Asn Gln Leu Ala Ala
                235                 240                 245

ggt ttt tct gat ggc tat cta gca ctt tgg aac atg aaa agc atg aaa      883
Gly Phe Ser Asp Gly Tyr Leu Ala Leu Trp Asn Met Lys Ser Met Lys
            250                 255                 260

aga gaa tat tac ata caa ttg gaa agt gga caa gtt cct gta tat gct      931
Arg Glu Tyr Tyr Ile Gln Leu Glu Ser Gly Gln Val Pro Val Tyr Ala
        265                 270                 275

gtc act ttt caa gaa cct gag aat gat cgt cgg aat tgc tgc tac ttg      979
Val Thr Phe Gln Glu Pro Glu Asn Asp Arg Arg Asn Cys Cys Tyr Leu
    280                 285                 290

tgg gct gtt cag tct aca caa gat agt gaa ggg gat gtt ttg agt ttg     1027
Trp Ala Val Gln Ser Thr Gln Asp Ser Glu Gly Asp Val Leu Ser Leu
295                 300                 305                 310

cat ctg ctg cag ctg gcc ttt ggt aat aga aag tgt ttg gca tca gga     1075
His Leu Leu Gln Leu Ala Phe Gly Asn Arg Lys Cys Leu Ala Ser Gly
                315                 320                 325

caa atc tta tat gag ggg tta gaa tac tgt gaa gaa aga tac acc ctg     1123
Gln Ile Leu Tyr Glu Gly Leu Glu Tyr Cys Glu Glu Arg Tyr Thr Leu
            330                 335                 340

gac ctg aca ggt ggc atg ttc cct ttg agg gga cag acg agt aat acc     1171
Asp Leu Thr Gly Gly Met Phe Pro Leu Arg Gly Gln Thr Ser Asn Thr
        345                 350                 355

aaa ttg ttg gga tgc cag agt ata gag aaa ttt cga tct cat ggt gac     1219
Lys Leu Leu Gly Cys Gln Ser Ile Glu Lys Phe Arg Ser His Gly Asp
    360                 365                 370

agg gag gaa ggc gtg aat gaa gct cta tcg cct gac act agt gtt tca     1267
Arg Glu Glu Gly Val Asn Glu Ala Leu Ser Pro Asp Thr Ser Val Ser
375                 380                 385                 390

gtc ttt acc tgg cag gtg aat ata tat gga cag gga aag cct tct gta     1315
Val Phe Thr Trp Gln Val Asn Ile Tyr Gly Gln Gly Lys Pro Ser Val
                395                 400                 405

tat ttg ggg ctt ttt gat ata aat cgt tgg tat cat gca caa atg cca     1363
Tyr Leu Gly Leu Phe Asp Ile Asn Arg Trp Tyr His Ala Gln Met Pro
            410                 415                 420

gat tcg tta agg tca gga gaa tat cta cat aat tgc tct tat ttt gca     1411
Asp Ser Leu Arg Ser Gly Glu Tyr Leu His Asn Cys Ser Tyr Phe Ala
        425                 430                 435

ctg tgg tca ttg gag tct gtt gta agt agg act tct cca cat ggc atc     1459
Leu Trp Ser Leu Glu Ser Val Val Ser Arg Thr Ser Pro His Gly Ile
    440                 445                 450

ttg gat ata tta gta cat gag aga agt tta aat aga gga gtc cct cct     1507
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Leu Asp Ile Leu Val His Glu Arg Ser Leu Asn Arg Gly Val Pro Pro
455                 460                 465                 470

tca tat cca cct ccc gag cag ttt ttt aat cca agc act tat aat ttt     1555
Ser Tyr Pro Pro Pro Glu Gln Phe Phe Asn Pro Ser Thr Tyr Asn Phe
                475                 480                 485

gat gcc act tgt ttg tta aac tcg gga gtt gtt cat tta act tgt act     1603
Asp Ala Thr Cys Leu Leu Asn Ser Gly Val Val His Leu Thr Cys Thr
            490                 495                 500

ggc ttt cag aag gag act ttg act ttt tta aag aaa tca ggt cca tca     1651
Gly Phe Gln Lys Glu Thr Leu Thr Phe Leu Lys Lys Ser Gly Pro Ser
        505                 510                 515

ctc aat gaa ctc att cct gat ggt tat aat cga tgt ctt gta gct ggc     1699
Leu Asn Glu Leu Ile Pro Asp Gly Tyr Asn Arg Cys Leu Val Ala Gly
    520                 525                 530

ctt ctt tcc cca aga ttt gtt gat gtt cag cct tcc agt tta agc caa     1747
Leu Leu Ser Pro Arg Phe Val Asp Val Gln Pro Ser Ser Leu Ser Gln
535                 540                 545                 550

gaa gaa cag tta gaa gct ata ttg tca gca gca att cag act agt tcc     1795
Glu Glu Gln Leu Glu Ala Ile Leu Ser Ala Ala Ile Gln Thr Ser Ser
                555                 560                 565

ctg gga ctt ttg act ggt tat atc cga aga tgg ata aca gaa gaa caa     1843
Leu Gly Leu Leu Thr Gly Tyr Ile Arg Arg Trp Ile Thr Glu Glu Gln
            570                 575                 580

cca aat tct gcc act aat ttg cgc ttt gtt ctt gaa tgg acg tgg aat     1891
Pro Asn Ser Ala Thr Asn Leu Arg Phe Val Leu Glu Trp Thr Trp Asn
        585                 590                 595

aaa gtg gtt ctc aca aaa gag gaa ttt gac aga cta tgt gtg cca tta     1939
Lys Val Val Leu Thr Lys Glu Glu Phe Asp Arg Leu Cys Val Pro Leu
    600                 605                 610

ttt gat ggt tcg tgt cat ttc atg gat cca caa act ata cag tct atc     1987
Phe Asp Gly Ser Cys His Phe Met Asp Pro Gln Thr Ile Gln Ser Ile
615                 620                 625                 630

cag caa tgc tat ttg ctt ctt agc aat ctt aat ata gtc ttg agc tgt     2035
Gln Gln Cys Tyr Leu Leu Leu Ser Asn Leu Asn Ile Val Leu Ser Cys
                635                 640                 645

ttt gca tca gaa gcc cga gag atc gct gag aga gga ctg ata gac tta     2083
Phe Ala Ser Glu Ala Arg Glu Ile Ala Glu Arg Gly Leu Ile Asp Leu
            650                 655                 660

agc aat aag ttt gtg gtt tcc cac ctc atc tgt cag tat gca caa gtg     2131
Ser Asn Lys Phe Val Val Ser His Leu Ile Cys Gln Tyr Ala Gln Val
        665                 670                 675

gtt ctt tgg ttc tct cat tct ggg ctt tta cca gaa ggc ata gat gat     2179
Val Leu Trp Phe Ser His Ser Gly Leu Leu Pro Glu Gly Ile Asp Asp
    680                 685                 690

tct gtg cag ttg tca agg tta tgc tac aac tac cct gta att cag aac     2227
Ser Val Gln Leu Ser Arg Leu Cys Tyr Asn Tyr Pro Val Ile Gln Asn
695                 700                 705                 710

tac tac acc agt cgt cga cag aag ttt gag cgt tta tca aga ggg aag     2275
Tyr Tyr Thr Ser Arg Arg Gln Lys Phe Glu Arg Leu Ser Arg Gly Lys
                715                 720                 725

tgg aat ccc gat tgc ttg atg att gat gga ctg gtt tct cag tta gga     2323
Trp Asn Pro Asp Cys Leu Met Ile Asp Gly Leu Val Ser Gln Leu Gly
            730                 735                 740

gag cga att gag aag ttg tgg aaa cga gat gaa gga ggc aca gga aaa     2371
Glu Arg Ile Glu Lys Leu Trp Lys Arg Asp Glu Gly Gly Thr Gly Lys
        745                 750                 755

tat cct cct gct agt ctg cat gca gta ctt gat atg tac cta tta gac     2419
Tyr Pro Pro Ala Ser Leu His Ala Val Leu Asp Met Tyr Leu Leu Asp
    760                 765                 770

ggc gtt act gaa gca gcc aaa cac tct att acc att tat ttg cta ctt     2467
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Gly Val Thr Glu Ala Ala Lys His Ser Ile Thr Ile Tyr Leu Leu Leu
775                 780                 785                 790

gat att atg tat tcc ttt ccc aac aaa aca gac act ccc att gaa tct     2515
Asp Ile Met Tyr Ser Phe Pro Asn Lys Thr Asp Thr Pro Ile Glu Ser
                795                 800                 805

ttc cca act gta ttt gcc att tct tgg ggc caa gtt aaa ctt att cag     2563
Phe Pro Thr Val Phe Ala Ile Ser Trp Gly Gln Val Lys Leu Ile Gln
            810                 815                 820

ggg ttt tgg ttg ata gat cat aat gac tat gag agt ggt ttg gat ctt     2611
Gly Phe Trp Leu Ile Asp His Asn Asp Tyr Glu Ser Gly Leu Asp Leu
        825                 830                 835

ttg ttt cat cca gct act gca aaa cct ttg tca tgg caa cat tca aag     2659
Leu Phe His Pro Ala Thr Ala Lys Pro Leu Ser Trp Gln His Ser Lys
    840                 845                 850

att att cag gca ttc atg agt cag ggc gag cac aga caa gcc ctc aga     2707
Ile Ile Gln Ala Phe Met Ser Gln Gly Glu His Arg Gln Ala Leu Arg
855                 860                 865                 870

tat att cag aca atg aag cca aca gtg tcc agt ggt aac gat gtt atc     2755
Tyr Ile Gln Thr Met Lys Pro Thr Val Ser Ser Gly Asn Asp Val Ile
                875                 880                 885

ctt cac ctc act gtt ttg ctt ttt aat agg tgt atg gtt gaa gcc tgg     2803
Leu His Leu Thr Val Leu Leu Phe Asn Arg Cys Met Val Glu Ala Trp
            890                 895                 900

aat ttt ttg cgg caa cat tgc aat agg ttg aat ata gag gag tta ctg     2851
Asn Phe Leu Arg Gln His Cys Asn Arg Leu Asn Ile Glu Glu Leu Leu
        905                 910                 915

aag cac atg tat gaa gtc tgt cag gaa atg ggc ttg atg gaa gat tta     2899
Lys His Met Tyr Glu Val Cys Gln Glu Met Gly Leu Met Glu Asp Leu
    920                 925                 930

ctg aag tta cca ttt aca gac act gag cag gaa tgt tta gtg aaa ttt     2947
Leu Lys Leu Pro Phe Thr Asp Thr Glu Gln Glu Cys Leu Val Lys Phe
935                 940                 945                 950

ttg cag tcc agt gcc agc gtt cag aat cat gaa ttc ctt tta gtg cac     2995
Leu Gln Ser Ser Ala Ser Val Gln Asn His Glu Phe Leu Leu Val His
                955                 960                 965

cat ttg cag cgt gcc aat tat gtg cct gcc ttg aag ctg aac caa act     3043
His Leu Gln Arg Ala Asn Tyr Val Pro Ala Leu Lys Leu Asn Gln Thr
            970                 975                 980

ctg aag att aat gtt atg aat gat cgt gat cct cgt ttg cgg gag aga     3091
Leu Lys Ile Asn Val Met Asn Asp Arg Asp Pro Arg Leu Arg Glu Arg
        985                 990                 995

tca ctg  gct cga aat tct ata  tta gac cag tat gga  aaa atc ctt      3136
Ser Leu  Ala Arg Asn Ser Ile  Leu Asp Gln Tyr Gly  Lys Ile Leu
    1000                1005                1010

cct aga  gtc cat cga aaa tta  gcc att gaa cga gct  aag cct tat      3181
Pro Arg  Val His Arg Lys Leu  Ala Ile Glu Arg Ala  Lys Pro Tyr
    1015                1020                1025

cat ctg  tca aca tca tca gtt  ttt cga tta gtt tct  aga ccc aaa      3226
His Leu  Ser Thr Ser Ser Val  Phe Arg Leu Val Ser  Arg Pro Lys
    1030                1035                1040

cca tta  tca gca gtt cca aag  caa gtt gta aca gga  act gtg ttg      3271
Pro Leu  Ser Ala Val Pro Lys  Gln Val Val Thr Gly  Thr Val Leu
    1045                1050                1055

aca aga  tct gtt ttc atc aac  aat gtg tta tct aaa  att gga gaa      3316
Thr Arg  Ser Val Phe Ile Asn  Asn Val Leu Ser Lys  Ile Gly Glu
    1060                1065                1070

gtt tgg  gca agc aaa gaa cct  ata aat agc acc aca  cct ttc aat      3361
Val Trp  Ala Ser Lys Glu Pro  Ile Asn Ser Thr Thr  Pro Phe Asn
    1075                1080                1085

agt tct  aaa ata gaa gaa cca  tct cct ata gtg tat  tcg ctc cca      3406
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Ser Ser  Lys Ile Glu Glu Pro  Ser Pro Ile Val Tyr  Ser Leu Pro
    1090                1095                1100

gct cca  gag ctg cct gag gca  ttt ttt gga aca cca  att tca aaa      3451
Ala Pro  Glu Leu Pro Glu Ala  Phe Phe Gly Thr Pro  Ile Ser Lys
    1105                1110                1115

gca tca  caa aaa att tct aga  ctg cta gat ttg gtt  gtt cag cct      3496
Ala Ser  Gln Lys Ile Ser Arg  Leu Leu Asp Leu Val  Val Gln Pro
    1120                1125                1130

gtc ccc  cgg cct tct cag tgt  tcg gag ttt att cag  caa agc tcc      3541
Val Pro  Arg Pro Ser Gln Cys  Ser Glu Phe Ile Gln  Gln Ser Ser
    1135                1140                1145

atg aaa  tct cct ttg tac cta  gta tcc cgt tca ctg  ccc tca agt      3586
Met Lys  Ser Pro Leu Tyr Leu  Val Ser Arg Ser Leu  Pro Ser Ser
    1150                1155                1160

tcg caa  tta aaa gga tcg cct  cag gcc atc tcc agg  gct tca gaa      3631
Ser Gln  Leu Lys Gly Ser Pro  Gln Ala Ile Ser Arg  Ala Ser Glu
    1165                1170                1175

tta cat  ttg ctt gaa act cct  ctt gta gtt aag aaa  gct aaa agt      3676
Leu His  Leu Leu Glu Thr Pro  Leu Val Val Lys Lys  Ala Lys Ser
    1180                1185                1190

ttg gcc  atg tca gtt act act  tct gga ttt tct gag  ttc act cct      3721
Leu Ala  Met Ser Val Thr Thr  Ser Gly Phe Ser Glu  Phe Thr Pro
    1195                1200                1205

cag tcc  atc ctg agg tct act  cct cga tca aca cct  tta gca tct      3766
Gln Ser  Ile Leu Arg Ser Thr  Pro Arg Ser Thr Pro  Leu Ala Ser
    1210                1215                1220

ccc tct  cca tca cct gga agg  tct cct caa cga ctt  aaa gaa act      3811
Pro Ser  Pro Ser Pro Gly Arg  Ser Pro Gln Arg Leu  Lys Glu Thr
    1225                1230                1235

aga att  tca ttt gtg gaa gaa  gat gtc cac cca aaa  tgg att cct      3856
Arg Ile  Ser Phe Val Glu Glu  Asp Val His Pro Lys  Trp Ile Pro
    1240                1245                1250

ggg gct  gca gat gat agc aaa  tta gaa gta ttt act  aca cct aaa      3901
Gly Ala  Ala Asp Asp Ser Lys  Leu Glu Val Phe Thr  Thr Pro Lys
    1255                1260                1265

aaa tgt  gca gtt cca gtg gaa  act gaa tgg ccg aag  agc aaa gat      3946
Lys Cys  Ala Val Pro Val Glu  Thr Glu Trp Pro Lys  Ser Lys Asp
    1270                1275                1280

agg acc  aca tct ttt ttc ctg  aac agc cct gaa aag  gag cat caa      3991
Arg Thr  Thr Ser Phe Phe Leu  Asn Ser Pro Glu Lys  Glu His Gln
    1285                1290                1295

gaa atg  gat gag ggg tca caa  agt tta gag aaa ctg  gat gtg agc      4036
Glu Met  Asp Glu Gly Ser Gln  Ser Leu Glu Lys Leu  Asp Val Ser
    1300                1305                1310

aaa gga  aac agc agt gtt tca  atc aca tcc gat gag  act acc tta      4081
Lys Gly  Asn Ser Ser Val Ser  Ile Thr Ser Asp Glu  Thr Thr Leu
    1315                1320                1325

gag tat  cag gat gca ccg tca  ccg gaa gac ctt gaa  gag act gtt      4126
Glu Tyr  Gln Asp Ala Pro Ser  Pro Glu Asp Leu Glu  Glu Thr Val
    1330                1335                1340

ttc acg  gcc tct aag ccc aaa  agc tct tcc act gca  cta act act      4171
Phe Thr  Ala Ser Lys Pro Lys  Ser Ser Ser Thr Ala  Leu Thr Thr
    1345                1350                1355

aat gta  act gaa caa act gaa  aag gat gga gat aaa  gat gta ttt      4216
Asn Val  Thr Glu Gln Thr Glu  Lys Asp Gly Asp Lys  Asp Val Phe
    1360                1365                1370

gca tca  gaa gta act cct tca  gac cta cag aaa caa  atg ggc aat      4261
Ala Ser  Glu Val Thr Pro Ser  Asp Leu Gln Lys Gln  Met Gly Asn
    1375                1380                1385

tta gaa  gat gca gaa aca aag  gat ctc tta gtt gca  gca gag gca      4306
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Leu Glu  Asp Ala Glu Thr Lys  Asp Leu Leu Val Ala  Ala Glu Ala
    1390                1395                1400

ttt tca  gaa ttg aat cac tta  agc ccg gtt caa gga  act gaa gct      4351
Phe Ser  Glu Leu Asn His Leu  Ser Pro Val Gln Gly  Thr Glu Ala
    1405                1410                1415

tct ctt  tgt gca cca tca gtc  tat gaa ggg aaa atc  ttc acc cag      4396
Ser Leu  Cys Ala Pro Ser Val  Tyr Glu Gly Lys Ile  Phe Thr Gln
    1420                1425                1430

aag tcc  aag gta cca gtg ttg  gac gaa gga tta aca  tct gtt gaa      4441
Lys Ser  Lys Val Pro Val Leu  Asp Glu Gly Leu Thr  Ser Val Glu
    1435                1440                1445

acc tac  acc cct gca att aga  gca aat gac aat aaa  tct atg gct      4486
Thr Tyr  Thr Pro Ala Ile Arg  Ala Asn Asp Asn Lys  Ser Met Ala
    1450                1455                1460

gat gtc  ctt ggt gat ggt gga  aac tcc tcg ctc act  atc tct gaa      4531
Asp Val  Leu Gly Asp Gly Gly  Asn Ser Ser Leu Thr  Ile Ser Glu
    1465                1470                1475

ggt cct  att gtc tct gag cgc  agg ctt aac cag gaa  gta gcg ctg      4576
Gly Pro  Ile Val Ser Glu Arg  Arg Leu Asn Gln Glu  Val Ala Leu
    1480                1485                1490

aac tta  aaa gaa gat cat gaa  gta gaa gtt ggt gta  cta aaa gaa      4621
Asn Leu  Lys Glu Asp His Glu  Val Glu Val Gly Val  Leu Lys Glu
    1495                1500                1505

agt gtt  gac tta cca gaa gaa  aag ctt cca att tct  gac agc cct      4666
Ser Val  Asp Leu Pro Glu Glu  Lys Leu Pro Ile Ser  Asp Ser Pro
    1510                1515                1520

cct gat  act caa gaa att cat  gtg att gaa caa gaa  aag ctt gaa      4711
Pro Asp  Thr Gln Glu Ile His  Val Ile Glu Gln Glu  Lys Leu Glu
    1525                1530                1535

gct caa  gat tca gga gaa gag  gct agg aat ctt tca  ttt aat gag      4756
Ala Gln  Asp Ser Gly Glu Glu  Ala Arg Asn Leu Ser  Phe Asn Glu
    1540                1545                1550

tta tat  ccc tct gga aca ctt  aag ctt cag tac aat  ttt gat act      4801
Leu Tyr  Pro Ser Gly Thr Leu  Lys Leu Gln Tyr Asn  Phe Asp Thr
    1555                1560                1565

att gac  caa cag ttt tgt gac  tta gct gat aac aaa  gac act gct      4846
Ile Asp  Gln Gln Phe Cys Asp  Leu Ala Asp Asn Lys  Asp Thr Ala
    1570                1575                1580

gaa tgt  gac att gct gaa gta  gat ggg gaa ctt ttt  gtg gct caa      4891
Glu Cys  Asp Ile Ala Glu Val  Asp Gly Glu Leu Phe  Val Ala Gln
    1585                1590                1595

agc aac  ttt acc ttg ata ttg  gaa ggt gaa gaa gga  gaa gtt gag      4936
Ser Asn  Phe Thr Leu Ile Leu  Glu Gly Glu Glu Gly  Glu Val Glu
    1600                1605                1610

cca ggt  gat ttt gca tca tct  gat gtg tta cct aaa  gca gct aac      4981
Pro Gly  Asp Phe Ala Ser Ser  Asp Val Leu Pro Lys  Ala Ala Asn
    1615                1620                1625

aca gca  act gaa gaa aaa ctt  gta tgc agt ggg gaa  aat gat aat      5026
Thr Ala  Thr Glu Glu Lys Leu  Val Cys Ser Gly Glu  Asn Asp Asn
    1630                1635                1640

cat gga  caa att gca aat ttg  cca tct gcc gta act  agt gac caa      5071
His Gly  Gln Ile Ala Asn Leu  Pro Ser Ala Val Thr  Ser Asp Gln
    1645                1650                1655

aag tcc  caa aaa gta gac act  tta cca tat gtg cct  gaa cct att      5116
Lys Ser  Gln Lys Val Asp Thr  Leu Pro Tyr Val Pro  Glu Pro Ile
    1660                1665                1670

aaa gta  gca att gca gaa aat  tta cta gat gta att  aaa gac aca      5161
Lys Val  Ala Ile Ala Glu Asn  Leu Leu Asp Val Ile  Lys Asp Thr
    1675                1680                1685

aga agt  aaa gaa att act tca  gat aca atg gaa cag  tcc att cat      5206
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Arg Ser  Lys Glu Ile Thr Ser  Asp Thr Met Glu Gln  Ser Ile His
    1690                1695                1700

gaa aca  ata cct tta gtg agc  caa aac ata atg tgt  ccc act aaa      5251
Glu Thr  Ile Pro Leu Val Ser  Gln Asn Ile Met Cys  Pro Thr Lys
    1705                1710                1715

ttg gtc  aaa tct gca ttt aag  act gct cag gaa aca  agc aca atg      5296
Leu Val  Lys Ser Ala Phe Lys  Thr Ala Gln Glu Thr  Ser Thr Met
    1720                1725                1730

act atg  aat gtc agc cag gtt  gat gac gtg gtt tcc  tcc aaa act      5341
Thr Met  Asn Val Ser Gln Val  Asp Asp Val Val Ser  Ser Lys Thr
    1735                1740                1745

cgt acg  aga ggt caa cgt atc  caa aac gtg aat gtc  aaa tca gca      5386
Arg Thr  Arg Gly Gln Arg Ile  Gln Asn Val Asn Val  Lys Ser Ala
    1750                1755                1760

caa cag  gaa gca tca gca gat  gtt gct act cct aag  atg cca ggg      5431
Gln Gln  Glu Ala Ser Ala Asp  Val Ala Thr Pro Lys  Met Pro Gly
    1765                1770                1775

cag tca  gtc agg aag aaa act  agg aag gca aaa gaa  att tct gaa      5476
Gln Ser  Val Arg Lys Lys Thr  Arg Lys Ala Lys Glu  Ile Ser Glu
    1780                1785                1790

gct tct  gaa aac atc tat tct  gat gtc aga gga cta  ttt cag aac      5521
Ala Ser  Glu Asn Ile Tyr Ser  Asp Val Arg Gly Leu  Phe Gln Asn
    1795                1800                1805

cag caa  ata cct caa aat tct  gtt acg cct agg aga  gga agg aga      5566
Gln Gln  Ile Pro Gln Asn Ser  Val Thr Pro Arg Arg  Gly Arg Arg
    1810                1815                1820

aag aaa  gaa gtt aat cag gac  ata cta gaa aac acc  agt tct gtg      5611
Lys Lys  Glu Val Asn Gln Asp  Ile Leu Glu Asn Thr  Ser Ser Val
    1825                1830                1835

gaa caa  gaa tta cag atc act  aca ggt agg gaa tca  aaa aga tta      5656
Glu Gln  Glu Leu Gln Ile Thr  Thr Gly Arg Glu Ser  Lys Arg Leu
    1840                1845                1850

aaa tca  tct cag ctg ttg gaa  cca gca gtt gaa gaa  act act aaa      5701
Lys Ser  Ser Gln Leu Leu Glu  Pro Ala Val Glu Glu  Thr Thr Lys
    1855                1860                1865

aaa gaa  gtt aag gtt tca tct  gtt aca aaa agg act  cct aga aga      5746
Lys Glu  Val Lys Val Ser Ser  Val Thr Lys Arg Thr  Pro Arg Arg
    1870                1875                1880

att aaa  aga tct gta gaa aat  cag gaa agt gtt gaa  att ata aat      5791
Ile Lys  Arg Ser Val Glu Asn  Gln Glu Ser Val Glu  Ile Ile Asn
    1885                1890                1895

gat cta  aaa gtt agt acg gta  aca agt cct agc aga  atg atc aga      5836
Asp Leu  Lys Val Ser Thr Val  Thr Ser Pro Ser Arg  Met Ile Arg
    1900                1905                1910

aaa ttg  aga agt act aat tta  gat gct tct gaa aat  aca gga aat      5881
Lys Leu  Arg Ser Thr Asn Leu  Asp Ala Ser Glu Asn  Thr Gly Asn
    1915                1920                1925

aag caa  gat gat aaa tcc agt  gac aag cag ctg cgt  att aaa cat      5926
Lys Gln  Asp Asp Lys Ser Ser  Asp Lys Gln Leu Arg  Ile Lys His
    1930                1935                1940

gtt aga  agg gtc aga ggg aga  gaa gtt agt cca tca  gat gtg aga      5971
Val Arg  Arg Val Arg Gly Arg  Glu Val Ser Pro Ser  Asp Val Arg
    1945                1950                1955

gaa gac  tcc aac ctt gag tca  tct cag ttg act gtt  caa gca gaa      6016
Glu Asp  Ser Asn Leu Glu Ser  Ser Gln Leu Thr Val  Gln Ala Glu
    1960                1965                1970

ttt gat  atg tct gcc ata cct  aga aaa cgt ggt aga  cca aga aaa      6061
Phe Asp  Met Ser Ala Ile Pro  Arg Lys Arg Gly Arg  Pro Arg Lys
    1975                1980                1985

atc aat  cca tct gaa gat gta  gga tct aag gct gtt  aag gaa gag      6106
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Ile Asn  Pro Ser Glu Asp Val  Gly Ser Lys Ala Val  Lys Glu Glu
    1990                1995                2000

aga agc  ccc aag aag aaa gaa  gct ccc agc att aga  agg aga tct      6151
Arg Ser  Pro Lys Lys Lys Glu  Ala Pro Ser Ile Arg  Arg Arg Ser
    2005                2010                2015

aca aga  aat acc cca gct aaa  agt gaa aat gtt gat  gtt gga aaa      6196
Thr Arg  Asn Thr Pro Ala Lys  Ser Glu Asn Val Asp  Val Gly Lys
    2020                2025                2030

cca gct  tta gga aaa tcc att  tta gtg cca aac gag  gaa ctt tcg      6241
Pro Ala  Leu Gly Lys Ser Ile  Leu Val Pro Asn Glu  Glu Leu Ser
    2035                2040                2045

atg gtg  atg agc tct aag aaa  aaa ctt aca aaa aag  act gaa agt      6286
Met Val  Met Ser Ser Lys Lys  Lys Leu Thr Lys Lys  Thr Glu Ser
    2050                2055                2060

caa agc  caa aaa cgt tca ttg  cac tca gta tca gaa  gaa cgc aca      6331
Gln Ser  Gln Lys Arg Ser Leu  His Ser Val Ser Glu  Glu Arg Thr
    2065                2070                2075

gat gaa  atg aca cat aaa gaa  aca aat gag cag gaa  gaa aga ttg      6376
Asp Glu  Met Thr His Lys Glu  Thr Asn Glu Gln Glu  Glu Arg Leu
    2080                2085                2090

ctc gcc  aca gct tcc ttc act  aaa tca tcc cgc agc  agc agg act      6421
Leu Ala  Thr Ala Ser Phe Thr  Lys Ser Ser Arg Ser  Ser Arg Thr
    2095                2100                2105

cgg tct  agc aag gcc atc ttg  ttg ccg gac ctt tct  gaa cca aac      6466
Arg Ser  Ser Lys Ala Ile Leu  Leu Pro Asp Leu Ser  Glu Pro Asn
    2110                2115                2120

aat gag  cct tta ttt tct cca  gcg tca gaa gtt cca  agg aaa gca      6511
Asn Glu  Pro Leu Phe Ser Pro  Ala Ser Glu Val Pro  Arg Lys Ala
    2125                2130                2135

aaa gct  aaa aaa ata gag gtt  cct gca cag ctg aaa  gaa tta gtt      6556
Lys Ala  Lys Lys Ile Glu Val  Pro Ala Gln Leu Lys  Glu Leu Val
    2140                2145                2150

tcg gat  tta tct tct cag ttt  gtc atc tca cct cct  gct tta agg      6601
Ser Asp  Leu Ser Ser Gln Phe  Val Ile Ser Pro Pro  Ala Leu Arg
    2155                2160                2165

agc aga  caa aaa aac aca tcc  aat aag aac aag ctt  gaa gat gaa      6646
Ser Arg  Gln Lys Asn Thr Ser  Asn Lys Asn Lys Leu  Glu Asp Glu
    2170                2175                2180

ctg aaa  gat gat gca caa tca  gta gaa act ctg gga  aag cca aaa      6691
Leu Lys  Asp Asp Ala Gln Ser  Val Glu Thr Leu Gly  Lys Pro Lys
    2185                2190                2195

gcg aaa  cga atc agg acg tca  aaa aca aaa caa gca  agc aaa aac      6736
Ala Lys  Arg Ile Arg Thr Ser  Lys Thr Lys Gln Ala  Ser Lys Asn
    2200                2205                2210

aca gaa  aaa gaa agt gct tgg  tca ctt cct ccc ata  gaa att cgg      6781
Thr Glu  Lys Glu Ser Ala Trp  Ser Leu Pro Pro Ile  Glu Ile Arg
    2215                2220                2225

ctg att  tcc ccc ttg gct agc  cca gct gac gga gtc  aag agc aaa      6826
Leu Ile  Ser Pro Leu Ala Ser  Pro Ala Asp Gly Val  Lys Ser Lys
    2230                2235                2240

cca aga  aaa act aca gaa gtg  aca gga aca ggt ctt  gga agg aac      6871
Pro Arg  Lys Thr Thr Glu Val  Thr Gly Thr Gly Leu  Gly Arg Asn
    2245                2250                2255

aga aag  aaa ctg tct tcc tat  cca aag caa att tta  cgc aga aaa      6916
Arg Lys  Lys Leu Ser Ser Tyr  Pro Lys Gln Ile Leu  Arg Arg Lys
    2260                2265                2270

atg ctg  taatttcttg ggaagatttt aatgtacacc tatttgtaaa gtcatcagaa     6972
Met Leu
    2275

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Syntheticaly generated peptide

<400> SEQUENCE: 16

Met Ala Ala Glu Arg Arg Cys Gly Ser
1 5

What is claimed is:

1. A purified polypeptide comprising the amino acid sequence of SEQ ID NO:14.

2. The polypeptide of claim **1**, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO: 14.

3. The polypeptide of claim **1**, wherein the polypeptide comprises the amino acid sequence encoded by position 98 to 6922 of the nucleic acid sequence of SEQ ID NO: 15.

4. The polypeptide of claim **1**, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 14 fused to a peptide or protein selected from the group consisting of FLAG, 6×His, 10×His, Influenza agglutinin (HA), human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, GST (glutathione-S-transferase), immunoglobulin constant region, β-galactosidase and MBP (maltose-binding protein).

5. A purified polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:14, wherein the fragment is at least 10% of the length of the sequence of SEQ ID NO: 14.

6. The polypeptide of claim **5**, wherein the fragment of the amino acid sequence of SEQ ID NO: 14 is fused to a peptide or protein selected from the group consisting of FLAG, 6×His, 10×His, Influenza HA, human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, GST, immunoglobulin constant region, β-galactosidase and MBP.

7. A purified polypeptide comprising the amino acid sequence from position 1 to 1137 of SEQ ID NO: 14.

8. The polypeptide of claim **7**, wherein the polypeptide consists of a fragment of the sequence of SEQ ID NO: 14, the fragment comprising the amino acid sequence from position 1 to 1137 of SEQ ID NO: 14.

9. The polypeptide of claim **7**, wherein the polypeptide comprises the amino acid sequence from position 1 to 1137 of SEQ ID NO: 14 fused to a peptide or protein selected from the group consisting of FLAG, 6×His, 10×His, Influenza HA, human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, GST, immunoglobulin constant region, β-galactosidase and MBP.

10. A purified polypeptide comprising the amino acid sequence from position 1684 to 2266 of SEQ ID NO: 14.

11. The polypeptide of claim **10**, wherein the polypeptide consists of a fragment of the sequence of SEQ ID NO: 14, the fragment comprising the amino acid sequence from position 1684 to 2266 of SEQ ID NO: 14.

12. The polypeptide of claim **10**, wherein the polypeptide comprises the amino acid sequence from position 1684 to 2266 of SEQ ID NO: 14 fused to a peptide or protein selected from the group consisting of FLAG, 6×His, 10×His, Influenza HA, human c-myc fragment, VSV-GP fragment, p18HIV fragment, T7-tag, HSV-tag, E-tag, SV40T antigen fragment, lck tag, α-tubulin fragment, B-tag, Protein C fragment, GST, immunoglobulin constant region, β-galactosidase and MBP.

13. A purified polypeptide consisting of a fragment of the amino acid sequence of SEQ ID NO: 14, wherein the fragment is at least 10% of the length of the sequence of SEQ ID NO: 14.

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